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(54) Title: METHOD AND SYSTEM FOR THE DETERMINATION OF GENE EXPRESSION IN M. CAPSULATUS

(57) Abstract: The invention related to method and systems for the determination of alteration of gene expression in M. capsulatus under a variery of conditions. A preferred embodiment of the invention relates to micro arrays comprising polynucleotides or oligonucleotides representative for a selective number of the genes of M. capsulatus.

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Method and system for the determination of gene expression in M. capsulatus

The present invention relates to methods and systems for the determination alteration of gene expression in M. capsulatus under a variety of conditions. A preferred embodiment of the invention relates to micro arrays comprising polynucleotides or oligonucleotides representative for a selective number or all of the genes of M. capsulatus.

The bacterium *M. capsulatus* is able to utilise methane as a single carbon and energy source. Bacteria capable of oxidising methane are collectively referred to as methanotrophs. They belong to different families and groups of the eubacteria but have in common the possession of the unusual enzyme methane monooxygenase, which catalyses the oxidation of methane to methanol.

The bacterium has an obligate requirement for methane or methanol and an optimum growth temperature of 45°C. Methane is oxidized via methanol to formaldehyde which is either assimilated into cellular biomass or dissimilated to carbon dioxide to release cellular energy.

M. capsulatus has a gram-negative cell envelope. Much of the intracellular space is occupied by an extensive

intracytoplasmic membrane system. The genome of *M. capsulatus* (Bath) has a molecular weight of 2.8 x 10^9 Da and a G+C content of 62.5 %.

Commercial interests involving *M. capsulatus* and other methanotrophs could roughly be divided into two categories: Those taking advantage of the inexpensive growth requirements of the bacteria and those taking advantage of unique catalytic activities possessed by the bacteria.

The development of high-cell density fermentation technology for *M. capsulatus* has created the possibility of producing large quantities of specialised compounds like for instance amino acids, cofactors, vitamins, metabolic end products, and various high value proteins, at reasonable costs.

Complete genomic sequencing will, in general, be useful for understanding the life cycle as well as important cellular process, of the organism in question. The function of many of the proteins could be identified by comparing with known protein sequences from other bacteria in the public sequence databases.

The inventors of the present invention have sequenced the M. capsulatus genome. One aspect of the present invention thus relates to novel genes and the proteins they code for. Their functions have been established by homology studies and will be further elucidated and confirmed by a number of experimental approaches.

Another important aspect of the present invention is to provide DNA micro arrays, which for instance can be used to study gene expression on a genomic scale. Such micro arrays make it easy to measure the transcript of a large number of the genes of M. capsulatus at once. Further, the tight connection between the function of a given gene product and its expression pattern can be determined. In relation to

the production of biomass from methane by the M. capsulatus bacterium, this is especially important since normally each gene is expressed under the specific conditions in which its products makes a contribution to the fitness and viability of the bacterium. Since protein synthesis in prokaryotes is directly coupled to mRNA synthesis, monitoring gene expression by array technology will provide information on the physiological status of the cells in culture. This will provide information relevant for controlling the culture conditions and thus the quality of the biomass produced. It will make it possible to identify subtle changes in the cell physiology important for the maintenance of optimal culture conditions.

"Biochips" or arrays of binding agents, such as oligonucleotides and peptides, have become an increasingly important tool in the biotechnology industry and related fields. These binding agent arrays, in which a plurality of binding agents are deposited onto a solid support surface in the form of an array or pattern, find use in a variety of applications, including drug screening, nucleic acid sequencing, mutation analysis, and the like. As indicated above, an important use of the biochips in accordance with the present invention is in the analysis of differential gene expression, where the expression of genes in different cells, normally a cell of interest and a control, is compared and any discrepancies in expression are identified. In such assays, the presence of discrepancies indicates a difference in the classes of genes expressed in the cells being compared.

In methods of differential gene expression, arrays find use by serving as a substrate to which is bound nucleic acid "probe" fragments. One then obtains "targets", for instance for the same bacterium but captured under different conditions. The targets are then hybridised to the immobilized set of nucleic acid "probe" fragments. Differences between the resultant hybridisation patterns

are then detected and related to differences in gene expression in the two sources.

A variety of different array technologies have been developed in order to meet the growing need of the biotechnology industry, as evidenced by the extensive number of patents and references within this field.

Despite the wide variety of array technologies currently in preparation or available on the market, there is a continued need to identify new array devices to meet the needs of specific research and industrial applications.

M. capsulatus arrays and kits, as well as methods for their preparation and use in hybridisation assays, are provided. The subject arrays have a plurality of probe polynucleotide spots each made up of unique polynucleotide(s) that corresponds to a M. capsulatus gene or gene sequence of interest. The subject arrays will find use in a wide range of applications, *inter alia* the expression analysis of the M. capsulatus genes.

The term "nucleic acid" as used herein means a polymer composed of nucleotides, e.g. deoxyribonucleotides or ribonucleotides.

The terms "ribonucleic acid" and "RNA" as used herein means a polymer composed of ribonucleotides.

The terms "deoxyribonucleic acid" and "DNA" as used herein means a polymer composed of deoxyribonucleotides.

The term "oligonucleotide" as used herein denotes single stranded nucleotide multimers of from about 10 to 100 nucleotides in length.

The term "polynucleotide" as used herein refers to single or double stranded polymer composed of nucleotide monomers

of greater than about 120 nucleotides in length up to about 1000 nucleotides in length.

"Key M. capsulatus genes" and are those genes that have been identified by those of skill in the art to play primary roles in a variety of different biological processes of the bacterium. Typically the M. capsulatus genes represented on the array are genes that are under tight transcriptional control. Key M. capsulatus genes of interest that may be represented on the array include: genes involved in metabolic pathways, genes involved in the synthesis of essential and non-essential compounds such as lipids, sterols, genes which are activated or deactivated with changes in environment of the M. capsulatus, and genes associated with different stages of the development of M. capsulatus

Specific M. capsulatus genes of interest include those listed in Tables 1 - 7, below. Further, also genes for which the function has not been identified may be of interest in an assay for the determination of differential expression. The present invention can thus use a selection of the genes presented in the accompanying sequence listing.

A gene is considered to be the same as a gene listed in one of the tables, or in the sequence listing, even if it:

(a) has a different name or accession number in a gene sequence database, e.g. GENBANK;

(b) has at least 80% homology (as determined using the FASTA program with default settings) to the sequence of one of the GENBANK accession numbers listed in the respective tables.

The "unique" polynucleotide sequences of each probe spot on the arrays of the subject invention are distinctive or different with respect to every other unique polynucleotide sequence on the arrays that corresponds to a key M.

capsulatus gene, as that term is defined herein. In other words, for at least 80% of the genes on the array, and more usually at least 90% of the genes on the array, any two different unique polynucleotides corresponding to a M. capsulatus gene on the array, (i.e. any two unique polynucleotides taken from different, non-identical spots on the array), are not homologous. By not homologous is meant that the sequence identity between the two given unique polynucleotides is less than about 90%, usually less than about 85% and more usually less than about 80% as measured by the FASTA program using default settings. Moreover, each polynucleotide sequence on the array is preferably statistically chosen to ensure that the probability of homology to any sequence of that type is very low. Further, each unique sequence on the array is preferably statistically chosen to insure that the probability of homology to any other known sequence associated with M. capsulatus genes is very low, whether or not the other sequence is represented on the array. An important feature of the individual polynucleotide probe compositions of the subject arrays is that they consist of only a fragment of the entire cDNA of the M. capsulatus gene to which they correspond. In other words, for each gene represented on the array, the entire cDNA sequence of the gene is not represented on the array. Instead, the sequence of only a portion (see further details below) or fragment of the entire cDNA is represented on the array by this unique polynucleotide. Two fundamentally different ways of designing these arrays are described below, i.e. 1) that each gene is represented by one polynucleotide molecule (preferable about 200 to 300 nt), and 2) that each gene is represented by a number of smaller polynucleotides, i.e. oligonucleotides of about 20 to 25 nt.

When using the larger polynucleotide fragments it is usually preferable to deposit PCT products of the isolated sequenced gene fragments. Probes used to retrieve the sequences can be designed by commercially available probe

design software (i.e. Oligo, GeneTool, and Gene Construction Kit).

The smaller oligonucleotides are preferably synthesized and thereafter deposited to the solid surface. Most preferable, such arrays are made by in situ synthesis of the oligonucleotides.

The term "polynucleotide probe composition" refers to the nucleic acid composition that makes up each of the probe spots on the array that correspond to a particular M. capsulatus gene. Thus, the term "polynucleotide (or oligonucleotide) probe composition" includes nucleic acid compositions of unique polynucleotides but excludes control or calibrating polynucleotides (e.g. polynucleotides corresponding to housekeeping genes), which may also be present on the array, as described in greater detail infra. The polynucleotide compositions are made up of single stranded polynucleotides (i.e. polynucleotides that are not hybridised to each other), where all of the polynucleotides in the probe composition may be identical to each other or there may be two or more different polynucleotides (i.e. polynucleotides of different nucleotide sequence) in each probe composition, e.g. where the two different polynucleotides are complementary to each other.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

M. capsulatus arrays, as well as methods for their preparation and use, are provided. In the subject M. capsulatus arrays, a plurality of polynucleotide probe spots is stably associated with the surface of a solid support. Each different polynucleotide probe spot is made up of a unique polynucleotide that corresponds to a key gene of interest. The subject arrays find particular use in gene expression assays of M. capsulatus genes.

In further describing the subject invention, the M. capsulatus arrays themselves are first discussed, followed by a description of methods for their preparation. The description is mainly based on the method of depositing polynucleotides on the solid surface, but a short description of the Affymetrixs' method is also given. It is also emphasized that the method and system according to the invention can be conducted with spotting unto a membrane as explained in the experimental section.

Next, a review of representative applications in which the subject arrays may be employed is provided.

It is to be understood that the invention is not limited to the particular embodiments of the invention described below, as variations of the particular embodiments may be made and still fall within the scope of the appended claims. It is also to be understood that the terminology employed is for the purpose of describing particular embodiments, and is not intended to be limiting. Instead, the scope of the present invention will be established by the appended claims.

In this specification and the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention belongs.

The arrays of the subject invention have a plurality of polynucleotide probe spots stably associated with a surface of a solid support. Each probe spot on the array comprises a polynucleotide probe sample or polynucleotide probe composition of known sequence and possible of known identity and function, as described in greater detail below. The polynucleotide probe spots on the array may be any convenient shape, but will typically be circular,

ellipsoid, oval, annular, or some other analogously curved shape, where the shape may, in certain embodiments, be a result of the particular method employed to produce the array. The density of the all of the spots on the solid surface, i.e. both probe spots and non-probe spots, e.g. calibration spots, control spots, etc., is at least about 5/cm^2 and usually at least about 10/cm^2 but does not exceed about 1000/cm^2.

The spots may be arranged in any convenient pattern across or over the surface of the array, such as in rows and columns so as to form a grid, in a circular pattern, and the like, where generally the pattern of spots will be present in the form of a grid across the surface of the solid support.

In the subject arrays, the spots of the pattern are stably associated with the surface of a solid support, where the support may be a flexible or rigid solid support. By stably associated is meant that the polynucleotides of the spots maintain their position relative to the solid support under hybridisation and washing conditions. As such, the polynucleotide members that make up the spots can be non-covalently or covalently stably associated with the support surface. Examples of non-covalent association include non-specific adsorption, binding based on electrostatic (e.g. ion, ion pair interactions), hydrophobic interactions, hydrogen bonding interactions, specific binding through a specific binding pair member covalently attached to the support surface, and the like. Examples of covalent binding include covalent bonds formed between the spot polynucleotides and a functional group present on the surface of the rigid support, e.g.—OH, where the functional group may be naturally occurring or present as a member of an introduced linking group, as described in greater detail below.

The array is present on either a flexible or rigid

substrate. By flexible is meant that the support is capable of being bent, folded or similarly manipulated without breakage. Examples of solid materials which are flexible solid supports with respect to the present invention include membranes, flexible plastic films, and the like. By rigid is meant that the support is solid and does not readily bend, i.e. the support is not flexible. As such, the rigid substrates of the subject arrays are sufficient to provide physical support and structure to the polymeric targets present thereon under the assay conditions in which the array is employed, particularly under high throughput handling conditions. Furthermore, when the rigid supports of the subject invention are bent, they are prone to breakage.

The solid supports upon which the subject patterns of spots are present in the subject arrays may take a variety of configurations ranging from simple to complex, depending on the intended use of the array. Thus, the substrate could have an overall slide or plate configuration, such as a rectangular or disc configuration.

The substrates of the subject arrays may be fabricated from a variety of materials. The materials from which the substrate is fabricated should ideally exhibit a low level of non-specific binding during hybridisation events. In many situations, it will also be preferable to employ a material that is transparent to visible and/or UV light. For flexible substrates, materials of interest include: nylon, both modified and unmodified, nitrocellulose, polypropylene, and the like, where a nylon membrane, as well as derivatives thereof, is of particular interest in this embodiment. For rigid substrates, specific materials of interest include: glass; plastics, e.g. polytetrafluoro-ethylene, polypropylene, polystyrene, polycarbonate, and blends thereof, and the like; metals, e.g. gold, platinum, and the like; etc.

The substrates of the subject arrays comprise at least one surface on which the pattern of probe spots is present, where the surface may be smooth or substantially planar, or have irregularities, such as depressions or elevations. The surface on which the pattern of spots is present may be modified with one or more different layers of compounds that serve to modify the properties of the surface in a desirable manner. Such modification layers, when present, will generally range in thickness from a monomolecular thickness to about 1 mm, usually from a monomolecular thickness to about 0.1 mm and more usually from a monomolecular thickness to about 0.001 mm. Modification layers of interest include: inorganic and organic layers such as metals, metal oxides, polymers, small organic molecules and the like. Polymeric layers of interest include layers of: peptides, proteins, polynucleic acids or mimetics thereof, e.g. peptide nucleic acids and the like; polysaccharides, phospholipids, polyurethanes, polyesters, polycarbonates, polyureas, polyamides, polyethyleneamines, polyarylene sulfides, polysiloxanes, polyimides, polyacetates, and the like, where the polymers may be hetero- or homopolymeric, and may or may not have separate functional moieties attached thereto, e.g. conjugated.

The total number of probe spots on the substrate will vary depending on the number of different polynucleotide probes one wishes to display on the surface, as may be desired depending on the particular application in which the subject arrays are to be employed. Generally, the pattern present on the surface of the array will comprise at least about 10 distinct spots, usually at least about 20 distinct spots, and more usually at least about 50 distinct spots, where the number of spots may be as high as 10,000 or higher, but will usually not exceed about 5,000 distinct spots, and more usually will not exceed about 3,000 distinct spots. In many embodiments, it is preferable to have each distinct probe composition presented in

duplicate, i.e. so that there are two spots for each distinct polynucleotide probe composition of the array.

The amount of polynucleotide present in each spot will be sufficient to provide for adequate hybridisation and detection of target nucleic acid during the assay in which the array is employed. Generally, the amount of polynucleotide in each spot will be at least about 0.1 ng, usually at least about 0.5 ng and more usually at least about 1 ng, where the amount may be as high as 1000 ng or higher, but will usually not exceed about 20 ng and more usually will not exceed about 10 ng. The copy number of each polynucleotide in a spot will be sufficient to provide enough hybridisation sites for target molecule to yield a detectable signal, and will generally range from about 0.01 fmol to 50 fmol, usually from about 0.05 fmol to 20 fmol and more usually from about 0.1 fmol to 5 fmol.

A critical feature of the subject arrays is that all of the probe polynucleotide spots of the array correspond to M. capsulatus genes of interest, particularly genes that have been identified by those of skill in the art to play primary roles in a variety of different biological processes of the M. capsulatus. Typically the genes represented on the array are genes that are under tight transcriptional control. As such, each polynucleotide probe spot on the array will preferable correspond to a key M. capsulatus gene of interest. Each probe spot on the array may correspond to a different M. capsulatus gene. Alternatively, two or more, usually no more than four, and more usually no more than three, different probe spots may correspond to the same gene, i.e. a gene may be represented by one or a plurality of different probe spots on the array. Furthermore, any given gene may be represented by two or more identical probe spots on the array, e.g. a particular probe spot may be presented on the array once or in duplicate, triplicate, etc, as mentioned above. The number of different genes represented on the array may

vary, where generally the number of different genes represented on the array will range from about 10 to 1000, usually from about 50 to 400 and more usually from about 100 to 300. A M. capsulatus gene is considered to be represented on a given array if a target nucleic acid derived from the M. capsulatus gene is able to hybridise to at least one probe spot on the array.

In one embodiment of the invention all of the genes sequenced in this project may be represented on a given array, thus making a total of about 3500 genes.

In an alternative embodiment, specific key M. capsulatus genes that may be represented on the arrays of the subject invention include those listed in table 1 to 7, respectively.

In one preferred embodiment, the subject array will include all of the genes listed in tables 1-7.

A further preferred embodiment includes genes given in the enclosed sequence listing, and the spotted sequences can also include unknown or unidentified genes, and preferable also genes unique to the M. capsulatus, for instance the genes listed in SEQ ID NO 374 to SEQ ID NO 1840.

The average length of the probe polynucleotides on the array is chosen to be of sufficient length to provide a strong and reproducible signal, as well as tight and robust hybridisation. As such, the average length of the polynucleotides of the array will typically range from about 120 to 1000 nt and usually from about 150 to 800 nt, where in many embodiments, the average length ranges from about 200 to 700 nt, and usually 200 to 600 nt. The length of each polynucleotide on the array is less than the length of the mRNA to which it corresponds. As such, the polynucleotide represents only a fraction of the full

length cDNA to which it corresponds.

The polynucleotide probe compositions that make up each spot on the array will be substantially, usually completely, free of non-nucleic acids, i.e. the probe compositions will not comprise non-nucleic acid biomolecules found in cells, such as proteins, lipids, and polysaccharides. In other words, the oligonucleotide spots of the arrays are substantially, if not entirely, free of non-nucleic acid cellular constituents. By substantially free is meant that the probe composition is at least about 90%, usually at least about 95% and more usually at least about 98% dry weight nucleic acid.

It should also be emphasized that the Affymetrix method can be used. This method uses multiple oligonucleotides of different sequence designed to hybridise to different regions of the same gene. Independent 25-mer oligonucleotides are selected (non-overlapping if possible, or minimally overlapping if necessary) to serve as sensitive, unique sequence-specific detectors.

As mentioned above, the subject arrays typically comprise one or more additional spots of polynucleotides which are not M. capsulatus genes. Other spots which may be present on the substrate surface include spots comprising genomic DNA, housekeeping genes, negative and positive control genes, and the like. These latter types of spots comprise polynucleotides that are not "unique" as that term is defined and used herein, i.e. they are "common." In other words, they are calibrating or control genes whose function is not to tell whether a particular M. capsulatus gene of interest is expressed, i.e. whether a particular M. capsulatus gene is expressed in a particular sample, but rather to provide other useful information, such as background or basal level of expression, and the like. For example, spots comprising genomic DNA may be provided in the array, where such spots may serve as orientation marks.

Spots comprising plasmid and bacteriophage genes, genes from the same or another species which are not expressed and do not cross hybridise with the cDNA target, and the like, may be present and serve as negative controls. Specific negative controls of interest include: M13 mp18(+) strand DNA, lambda DNA and pUC 18. In addition, spots comprising housekeeping genes and other control genes from the same or another species may be present, which spots serve in the normalization of mRNA abundance and standardization of hybridisation signal intensity in the sample assayed with the array.

Each probe spot of the pattern present on the surface of the substrate is made up of a unique polynucleotide probe composition. By "polynucleotide probe composition" is meant a collection or population of single stranded polynucleotides capable of participating in a hybridisation event under appropriate hybridisation conditions, where each of the individual polynucleotides may be the same, have the same nucleotide sequence, or have different sequences, for example the probe composition may consist of 2 different single stranded polynucleotides that are complementary to each other (i.e. the two different polynucleotides in the spot are complementary but physically separated so as to be single stranded, i.e. not hybridised to each other). In many embodiments, the probe compositions will comprise two complementary, single stranded polynucleotides.

In the polynucleotide probe compositions, the sequence of the polynucleotides are chosen so that each distinct unique polynucleotide does not cross-hybridise with any other distinct unique polynucleotide of another probe spot on the array, i.e. the polynucleotide of any other polynucleotide composition that corresponds to a M. capsulatus gene. As such, the nucleotide sequence of each unique polynucleotide of a probe composition will have less than 90% homology, usually less than 85% homology, and more usually less than

80% homology with any other different polynucleotide of a probe composition of the array, where homology is determined by sequence analysis comparison using the FASTA program using default settings. The sequence of unique polynucleotides in the probe compositions are not conserved sequences found in a number of different genes (at least two), where a conserved sequence is defined as a stretch of from about 40 to 200 nucleotides which have at least about 90% sequence identity, where sequence identity is measured as above. The polynucleotide will not cross-hybridise with any other polynucleotide on the array under standard hybridisation conditions. Again, the length of the polynucleotide will be shorter than the mRNA to which it corresponds.

The subject arrays can be prepared using any convenient means. As indicated above the isolated and PCR amplified gene fragments can be deposited on the solid surface.

Another means of preparing the subject arrays is to first synthesize the polynucleotides for each spot and then deposit the polynucleotides as a spot on the support surface. The polynucleotides may be prepared using any convenient methodology, such as automated solid phase synthesis protocols, restriction digestion of a gene fragment insert cloned into a vector, preparative PCR and like, where preparative PCR or enzymatic synthesis is preferred in view of the length and the large number of polynucleotides that must be generated for each array. In the case of automated solid phase synthesis, each polynucleotide can be represented by several overlapping or non-overlapping oligonucleotides from 10 to 100 nucleotides in length, which cover all or a partial sequence of a gene or polynucleotide.

For preparative PCR, primers flanking either side of the portion of the gene of interest will be employed to produce amplified copy numbers of the portion of interest. Methods

of performing preparative PCR are well known in the art. Alternatively, if a gene fragment of interest is cloned into a vector, vector primers can be used to amplify the gene fragment of interest to produce the polynucleotide.

In determining the portion of the gene to be amplified and subsequently placed on the array, regions of the gene having a sequence unique to that gene should preferably be amplified. Different methods may be employed to choose the specific region of the gene to be amplified. Thus, one can use a random approach based on availability of a gene of interest. However, instead of using a random approach which is based on availability of a gene of interest, a rational design approach may also be employed to choose the optimal sequence for the hybridisation array. Preferably, the region of the gene that is selected and amplified is chosen based on the following criteria. First, the sequence that is chosen should yield a polynucleotide that does not cross-hybridise with any other polynucleotide that is present on the array. Second, the sequence should be chosen such that the polynucleotide has a low probability of cross-hybridising with a polynucleotide having a nucleotide sequence found in any other gene, whether or not the gene is to be represented on the array. As such, sequences that are avoided include those found in: highly expressed gene products, structural RNAs, repeated sequences found in the sample to be tested with the array and sequences found in vectors. A further consideration is to select sequences that provide for minimal or no secondary structure, structure which allows for optimal hybridisation but low non-specific binding, equal or similar thermal stabilities, and optimal hybridisation characteristics.

The prepared polynucleotides may be spotted on the support using any convenient methodology, including manual techniques, e.g. by micropipette, ink jet, pins, etc., and automated protocols. Of particular interest is the use of an automated spotting device, such as the Beckman Biomek

2000 (Beckman Instruments). As mentioned above, the polynucleotide probe compositions that are spotted onto the array surface are made up of single stranded polynucleotides, where all the polynucleotides may be identical to each other or a population of complementary polynucleotides may be present in each spot.

The subject arrays find use in a variety of different applications in which one is interested in detecting the occurrence of one or more binding events between target nucleic acids and probes on the array and then relating the occurrence of the binding event(s) to the presence of a target(s) in a sample, i.e. the expression of a particular key M. capsulatus gene in a sample. In general, the device will be contacted with the sample suspected of containing the target gene under conditions sufficient for binding of any target present in the sample to a complementary polynucleotide present on the array. Generally, the sample will be a fluid sample and contact will be achieved by introduction of an appropriate volume of the fluid sample onto the array surface, where introduction can via inlet port, deposition, dipping the array into a fluid sample, and the like.

Targets may be generated by methods known in the art. mRNA can be labelled and used directly as a target, or converted to a labelled cDNA target. Generally, such methods include the use of oligonucleotide primers. Primers that may be employed include oligo dT, random primers, e.g. random hexamers and gene specific primers. Where gene specific primers are employed, the gene specific primers are preferably those primers that correspond to the different polynucleotide spots on the array. Thus, one will preferably employ gene specific primers for each different polynucleotide that is present on the array, so that if the gene is expressed in the particular cell or tissue being analysed, labelled target will be generated from the sample for that gene. In this manner, if a particular key M.

capsulatus gene present on the array is expressed in a particular sample, the appropriate target will be generated and subsequently identified.

A variety of different protocols may be used to generate the labelled target nucleic acids, as is known in the art, where such methods typically rely on the enzymatic generation of the labelled target using the initial primer. Labelled primers can be employed to generate the labelled target. Alternatively, label can be incorporated during first strand synthesis or subsequent synthesis, labelling or amplification steps in order to produce labelled target. Alternatively, the label can be introduced by chemical cDNA synthesis.

As mentioned above, following preparation of the target nucleic acid from the tissue or cell of interest, the labelled target nucleic acid is then contacted with the array under hybridisation conditions, where such conditions can be adjusted, as desired, to provide for an optimum level of specificity in view of the particular assay being performed. Suitable hybridisation conditions are well known to those of skill in the art, e.g. stringent conditions (e.g. at 50 °C. or higher and 0.1 X SSC (15 mM sodium chloride/01.5 mM sodium citrate). In analysing the differences in the population of labelled target nucleic acids generated from two or more physiological sources using the arrays described above, each population of labelled target nucleic acids are separately contacted to identical probe arrays or together to the same array under conditions of hybridisation, preferably under stringent hybridisation conditions, such that labelled target nucleic acids hybridise to complementary probes on the substrate surface.

Where all of the target sequences comprise the same label, different arrays will be employed for each physiological source (where different could include using the same array

at different times). Alternatively, where the labels of the targets are different and distinguishable for each of the different physiological sources being assayed, the opportunity arises to use the same array at the same time for each of the different target populations. Examples of distinguishable labels are well known in the art and include: two or more different emission wavelength fluorescent dyes, like Cy3 and Cy5, two or more isotopes with different energy of emission, like ^{32}p and ^{33}p, light scattering particles with different scattering spectra, labels which generate signals under different treatment conditions, like temperature, pH, treatment by additional chemical agents, etc., or generate signals at different time points after treatment. Using one or more enzymes for signal generation allows for the use of an even greater variety of distinguishable labels, based on different substrate specificity of enzymes (alkaline phosphatase/ peroxidase).

Following hybridisation, non-hybridised labelled nucleic acid is removed from the support surface conveniently by washing, generating a pattern of hybridised nucleic acid on the substrate surface. A variety of wash solutions are known to those of skill in the art and may be used.

The resultant hybridisation patterns of labelled nucleic acids may be visualized or detected in a variety of ways, with the particular manner of detection being chosen based on the particular label of the target nucleic acid, where representative detection means include scintillation counting, autoradiography, fluorescence measurement, calorimetric measurement, light emission measurement, light scattering and the like.

Following detection or visualization, the hybridisation patterns may be compared to identify differences between the patterns. Where arrays in which each of the different probes corresponds to a known gene are employed, any

discrepancies can be related to a differential expression of a particular gene in the physiological sources being compared.

Also provided are kits for performing analyte binding assays using the subject devices, where kits for carrying out differential gene expression analysis assays are preferred. Such kits according to the subject invention will at least comprise a M. capsulatus array according to the subject invention. The kits may further comprise one or more additional reagents employed in the various methods, such as primers for generating target nucleic acids, dNTPs and/or rNTPs, which may be either premixed or separate, one or more uniquely labeled dNTPs and/or rNTPs, such as biotinylated or Cy3 or Cy5 tagged dNTPs, or other post synthesis labeling reagent, such as chemically active derivatives of fluorescent dyes, biotin, digoxigenin, or strept/avidin-label conjugate or antibody-label conjugate, enzymes, such as reverse transcriptases, DNA polymerases, and the like, various buffer mediums, e.g. hybridisation and washing buffers, labelled target purification reagents and components, like spin columns, etc., signal generation and detection reagents, e.g streptavidin-alkaline phosphatase conjugate, chemifluorescent or chemiluminescent substrate, and the like.

In addition to the DNA arrays, the present invention also related to a kit for use in a hybridisation assay, said kit comprising a DNA array according to one the present invention. The kit preferable contains reagents for generating a labelled target polynucleotide sample, a hybridisation buffer and a wash medium.

Further, the present invention related to novel DNA molecules selected from the group comprising SEQ ID NO 1 to SEC ID NO 373, and also to the protein for which these genes codes.

A further embodiment of the present invention related to a method or the determination of the differential expression of the genes of M. capsulatus due to an alteration in the incubation conditions from a firs incubation condition to a second incubation condition, wherein the expression of a plurality of sequences from the group comprising SEQ ID NO 1 to SEQ ID NO 454, and preferable also SEQ ID NO 455 - 1840, is monitored on the two respective DNA arrays, and where expression of the first incubation condition is compared with the expression of the same genes of the second incubation condition.

Preferable, the alteration of incubation condition is selected from the group comprising alteration in temperature, alteration in pH, alteration in the presence of other organisms, the presence of chemicals, the presence of toxins, alteration in carbon source, alteration in energy source, alteration in trace element source, alteration in nitrogen source, alteration in phosphorous source and alterations in sulphur source.

A preferable embodiment relates to the monitoring of expression as a result of various concentrations of copper ions.

The following examples are offered by way of illustration and not by way of limitation.

EXAMPLE 1

Sequencing of the M. Capsulatus genome

Methylococcus capsulatus Bath NCIMB 11182 was purchased from NCIMB Ltd. (Aberdeen, UK) and grown in a medium described by Whittenbury (1970) on methane or methanol as sole carbon and energy source. Chromosomal DNA was extracted and purified after a method of Marmur (Johnson, 1994). Two plasmid libraries, BMC and BMD, using the

vectors pHOS1 or pHOS2 were constructed with an average insert size of 2 and 10 kB respectively. The genomic DNA was mechanically sheared to the decided range. The DNA fragments where then made blunt-ended and adapters were ligated to the ends before ligation into the vectors. Whole genome random sequencing and assembly of individual sequences where done as described by Fraser et al. (1997). A total of 6- and 2-times coverage of the genome will be sequenced from BMC and BMD, respectively.

EXAMPLE 2

Generation of an array system for the determination of different expression at low and high concentraion of copper.

Culture conditions (fermentor)

Methylococcus capsulatus (Bath) NCIMB 11132 was grown in continuous cultures (2L) supplied by ammonium nitrate/mineral salts (NMS) medium, with methane as the source of carbon and energy. An atmosphere of air/methane was maintained in ratio of 5:1, and the temperature of growth was 45°C. The initial concentration of copper supplied to the culture was 0.25 mg/L $CuSO_4 \cdot 5H_2O$. When the cell density reached OD≈6.5, the amount of copper in the fermentor was gradually diluted, by supplying the fermentor with NMS medium lacking copper (<1mg/L copper). Collected samples were screened for the activity of sMMO by use of an enzymatic assay based on that reported by Brusseau et al. (1990).

RNA work

Samples were harvested just before changing medium at an OD of 6.16 and after 3 days of growth in copper free medium. The copper switch was indicated by the absence of sMMO activity in the latter sample. Total RNA were extracted using the hot-phenol method as described in Nielsen et.al, 1996 Microbiology.

The RNA probes were labelled with P^{32} using the GenomeDirectedPrimers given in table 1, and purified on columns. 40 8'mer primers label ~80% of the *M.capsulatus* estimated transcripts

Table 1

M. capsulatus Genome Directed Primers

1GDP-MC-R	CGCCGCCG
2GDP-MC-R	CGGCGGCG
3GDP-MC-R	CCGCCGCC
4GDP-MC-R	CGGCGCCG
5GDP-MC-R	CGCCGGCG
6GDP-MC-R	GCCGCCGG
7GDP-MC-R	GCCGCCGC
8GDP-MC-R	CGATGCCG
9GDP-MC-R	GGCGGCGG
10GDP-MC-R	CCGCCGGC
11GDP-MC-R	GCGGCGGC
12GDP-MC-R	GGCGGCGA
13GDP-MC-R	CCGGCGGC
14GDP-MC-R	CCGCCAGC
15GDP-MC-R	CCGGCGCC
16GDP-MC-R	CGGCCAGC
17GDP-MC-R	GCCGGCGG
18GDP-MC-R	GCCGGCGC
19GDP-MC-R	CCAGCGCC
20GDP-MC-R	CGGCCGGC
21GDP-MC-R	GGCCGGCG
22GDP-MC-R	CGCCGGCC
23GDP-MC-R	GCGCCGGC
24GDP-MC-R	CGGCGATG
25GDP-MC-R	CGATGGCG
26GDP-MC-R	CCGCGCCG
27GDP-MC-R	GCCGGCGA
28GDP-MC-R	CGGCATCG
29GDP-MC-R	GCCGGCCG

30GDP-MC-R	GGCCGCCG
31GDP-MC-R	TCGGCCAG
32GDP-MC-R	CGGCGCGG
33GDP-MC-R	GCCGCGGC
34GDP-MC-R	CGGCCGCC
35GDP-MC-R	CGGCTTCG
36GDP-MC-R	GCCCGCCG
37GDP-MC-R	CGGCGATC
38GDP-MC-R	GATGCCGG
39GDP-MC-R	CCAGCCGC
40GDP-MC-R	CCAGCCGG

Dot-Blot assay

PCR products were amplificated from *M.capsulatus* genomicDNA using the listed primers. The specific primers for PCR amplification was designed to amplify 100-400 bp PCR products from each of the ORF of interest. The ORFs are given in table 3.

Table 2

ORF spesific primers used to amplify the templat PCR products making up the array.

>26 ABC-type transport protein sll0739 - Synechocystis sp:
F2 26-F(254): GCAGCCTATGTGTTTCAAGACTACG (254)
R7 26-R(438): CCGGAGAGTTCGTTCGGATAC (438)

>564 HYPOTHETICAL ABC TRANSPORTER ATP-BINDING PROTEIN YHIH:
F5 564-F(1121): GTCAACGCCTTGTCCTTGATTG (1121)
R1 564-R(1398): CAGGAAGTCGGAAACCCGTAG (1398)

>83 LIPOPROTEIN RELEASING SYSTEM ATP-BINDING PROTEIN LOLD:
F1 83-F(258): GTCTATCAGCTCATGCTGGAGCTC (258)
R1 83-R(369): CATCCTCCATGTGGAGGACCT (369)

>1987 SecA [Pasteurella multocida]:
F4 1987-F(200): CTCACTGGAAGATCCCCTCATG (200)
R1 1987-R(544): ACATCCCACTGTTCCTCGAGG (544)

>723 TRIOSEPHOSPHATE ISOMERASE (TIM):
F9 723-F(29): TCATGTTTTGCTCGCCTTGAG (29)
R1 723-R(232): TGACCGGACAGATAAGCAAGAGTC (232)

>732 queuine tRNA-ribosyltransferase:

F5 732-F(15): AGTTTCTTTATTGCCGACGCCT (15)
R1 732-R(202): GTGACCACTTCAACCCCCTTG (202)

>734 general protein secretion pathway subunit SecD:
F2 734-F(157): CATCGAGAACAAGTCCGAGACC (157)
R6 734-R(482): GGCCGAACATCCGGTAATAGAG (482)

>3263 protein-transport protein SecB VC2653:
F2 3263-F(65): AAGGACGTATCGTTCGAGACCC (65)
R2 3263-R(370): TTTGTTCACGAGATCCGAGACC (370)

>3490 copper export protein homolog ycnJ - Bacillus subtilis:
F4 3490-F(638): CATCTTCCTGACCGGTATGTGTCT (638)
R1 3490-R(932): GCGCTGAGGACTGGAAACATATAG (932)

>1344 SHIKIMATE 5-DEHYDROGENASE:
F3 1344-F(95): GGCCAGGACCTGATCTACACC (95)
R1 1344-R(389): GTATGAGGATTTTCGTGCCCG (389)

>960 exopolyphosphatase XF2590 [imported]:
F6 960-F(2): TATTTGTATCAGAACCCTCCCGC (2)
R1 960-R(432): AGATAGGTCAGACGGGCCTCC (432)

>2756 gluconate-6-phosphate dehydrogenase [Escherichia coli]:
F1 2756-F(944): GATTCCTGGTCGACAAGGTCCT (944)
R1 2756-R(1224): CCATGAGTTGGAAACCTTGGG (1224)

>2759 SucA [Pasteurella multocida] :
F2 2759-F(2026): ACGGTTACAGCAGCTCGGAAC (2026)
R1 2759-R(2511): TTTCCAGCAGGTCGTAATAGACCTT (2511)

>2760 SucB [Pasteurella multocida]:
F2 2760-F(392): GTTGGTGATGGTGAAGGTCCC (392)
R3 2760-R(593): CGAGGAAATCGTCTACCACGACTA (593)

>2761 polyphosphate kinase [Caulobacter crescentus]:
F1 2761-F(122): GATCTTTTCGGTCGAGGAGCTC (122)
R1 2761-R(470): TTCGAAGAACTCATCCATATTGGAAC (470)

>246 methanol dehydrogenase alpha subunit
F5 246-F(878) : TCGATACCGGTGAAGCCAAGT (878)
R2 246-R(1018): AGTGGGTCAGCAGCTTGGAGT (1018)

>3530 methanol dehydrogenase alpha subunit:
F3 3530-F(1016): CAGGTCGAATACCAGCCCTACTC (1016)
R1 3530-R(1335): AACATGTATCCGGACCCAAGG (1335)

>242 particulate methane monooxygenase subunit PmoC3:
F1 242-F(394): TCTACTGGGGCGCATCCTACT (394)
R2 242-R(525): AACCGGTGATGATGTAGATCGG (525)

>1415 probable methane monooxygenase 45k chain - Methylococcus capsulatus:
F2 1415-F(926) : GACAACCCGGAAGTCATAGGTCTT (926)
R2 1415-R(1151): GAGCTGGTCGAAAGAGAAAGTCAAG (1151)

>1416 probable methane monooxygenase 27k chain - Methylococcus capsulatus:

F1 1416-F(117): GTTTTTCGTGATCGTGGGCTC (117)
R2 1416-R(382): AAGTTGATCGGGAAGTAGGTCCA (382)

>1417 particulate methane monooxygenase subunit PmoC3:
F3 1417-F(66) : CCGGAGTTCGAGACCTACTGG (66)
R1 1417-R(286): TCCTGCTCGGTGAAGTAGGATG (286)

>3126 soluble methane monooxygenase protein A alpha subunit:
F1 3126-F(270): CGCCAAGTATCTCAACACGGA (270)
R12 3126-R(645): CTCGTAGATCTTGCCGTAGTGGTC (645)

>3127 soluble methane monooxygenase protein A beta subunit:
F2 3127-F(810) : GACGAACGGGGAGGTCTACAA (810)
R1 3127-R(1269): GATCCTGCTGGCGTAGTCCTC (1269)

>3128 methane monooxygenase A beta chain [Methylococcus:
F1 3128-F(333): CGTTCCAGTCGAACACCTCCT (333)
R2 3128-R(631): GTTCATCAACCGGTATTGGGG (631)

>3049 MopB [Methylococcus capsulatus]:
F5 3049-F(123): CGCGGAGTACACCTATACGGG (123)
R1 3049-R(352): GCTGGAACGCATCCCTAGAAA (352)

>3337 transposase [Acidovorax avenae subsp. citrulli]:
F5 3337-F(128): TTGTCCATGAGGATGTGACCC (128)
R2 3337-R(512): GCCTGAACCTGGAAGACAAGG (512)

>3340 transposase [Xanthomonas axonopodis pv. dieffenbachiae]:
F1 3340-F(497): GCTGGAACCACAAACGTGTGT (497)
R1 3340-R(732): GAAGTCCACCTCCATCCCTAGC (732)

>1020 putative cation-transporting ATP-ase - copper transport:
F2 1020-F(317): TATTGGTCATCGCCTGTCCCT (317)
R2 1020-R(733): ACTTTTCCATCATGGCCACGT (733)

The specific primers were applied to the Hybond N+ membrane. The membrane was pre-wetted with distilled water and treated with 10 x SSC, and placed on a vacuum blotter. 4 ul of the denatured DNA sample is applied to each spot on the membrane. The membrane was placed onto a 3mm paper pre-wet in denaturation solution: 1.5 M NaCl, 0.5 M NaOH for 3 min, the 3 mm paper was changed, and the process repeated. The membrane was thereafter placed onto a 3 mm paper pre-wet in neutralisation solution: 1.5 M NaCl, 0.5 M TrisHCl (7.2) for 3 min. The paper was changed, and the method repeated. The membrane was then placed onto a dry 3mm

paper. After that, the membrane was radiated with UV-light for 2 min.

Hybridisation

The membrane was pre-hybridisated at 65 °C for 5 h with the pre-hybridisation solution: 3 ml 20 x SSC, 1.2 ml 50 x Denhards solution, 0.12 ml sperm DNA, 1.12 ml 10 % SDS and 6,5 ml H_2O.

Thereafter the membrane was hybridised with the labelled cDNA probes made using the GDP primers in table 1 over night. The membranes were washed 3 x 20 min with Wash solution 1: 20 ml 20 x SCS, 10 ml 20 % SDS and 170 ml H_2O, and 2 x 20 min with washing solution 2: 0.5 ml 20 x SCS, 2.5 ml 20 % SDS and 97 ml H_2O.

The membranes were developed onto a imigar film, and scanned in the phosphoimigar.

Results

The figure shows the different of mRNA expression levels of the genes from cells grown under different concentrations of copper. It is evident that the expression levels are different in the two culture systems, and this clearly indicates that the method and system according to the invention is suited for the determination of differential expression levels.

EXAMPLE 3

Generation of a general M. capsulatus DNA array

An embodiment of the invention relates to a DNA array where substantially all of the M. capsulatus genes, about 3500 genes, were isolated and amplified in separate test tubes using a combination of sense and antisense gene-specific primers capable of amplifying the gene fragments of interest. Some of these genes are given in the tables 1 - 7, below. This array can be made by prior art methods (design and synthesis of specific primers, amplification, deposition on solid support etc.) known for a person skilled in the art.

EXAMPLE 4

DNA array for the measurement of key metabolic features

A selection of genes involved in the metabolism of carbon and nitrogen are incorporated to this embodiment of a DNA array. Some of these genes are given in table 1, below. A selection of genes involved in the energy metabolism are given in table 2, below, and genes involved in the metabolism of lipids are given i table 3. Other metabolic important genes are given in table 4, for instance genes involved in the serine and butanediol pathways.

EXAMPLE 5

DNA array comprising M. capsulatus regulator genes.

An embodiment of the invention relates to a DNA array containing a number of genes anticipated to play a function in the regulation of the M. capsulatus, and a selection of some of these genes are given in table 5, below.

EXAMPLE 6

DNA array comprising M. capsulatus genes involved in transport and secretion.

An embodiment of the invention relates to a DNA array containing a number of genes anticipated to play a function in transportation and secretion, and a selection of some of these genes are given in table 6, below.

EXAMPLE 7

DNA array comprising M. capsulatus genes with unknown function.

An embodiment of the invention relates to a DNA array containing a number of genes wherefore the function still remains to be established. These genes are given as SEQ ID NO 374 to SEQ ID NO 1840.

It is highly emphasized that both groups of genes, i.e. group (a) and (b) can be incorporated on the same DNA array, and that this DNA array also may contain several of the genes of tables 1 - 7 for which a putative function have been assigned.

Table 1
Genes involved in the metabolism of carbon and nitrogen

SEQ ID NO	Putauve names
3	98 RBCR_CHRVI (P25544) RUBISCO OPERON TRANSCRIPTIONAL REGULATOR
18	422 GARR_ECOLI (P23523) 2-HYDROXY-3-OXOPROPIONATE REDUCTASE
19	427 SPEE_METJA (Q57761) PROBABLE SPERMIDINE SYNTHASE
22	444 bmc_12 nitrate-inducible formate dehydrogenase, gamma subunit 5750-6400
23	445 bmc_12 Formate Dehydrogenase-O, Iron-Sulfur Subunit
24	449 bmc_12 Formate Dehydrogenase-O, Major Subunit (Formate Dehydrogenase-O Alpha Subunit
28	549 PmoC3 (-1), bmc_16, 795
29	633 bmc_20 (AJ011927) fructose-1,6-bisphosphate aldolase 0-1200
45	792 Bmc_24 Probable Methane Monooxygenase 45k Chain - Methylococcus
46	793 Bmc_24 PmoA2 31900-32500
47	795 Bmc_24 PmoC2 691 siste i contig
53	831 Bmc_26 acetate kinase 6500-7
73	1350 CSTA_ECOLI (P15078) CARBON STARVATION PROTEIN A
96	2064 CSRA_PSEAE (O69078) CARBON STORAGE REGULATOR HOMOLOG
101	2241 bmc_57 nifA 12500-14100
103	2271 bmc_57 Methanol Dehydrogenase Subunit 1 Precursor
106	2339 Bmc_60 moxR protein - Deinococcus radiodurans
111	2459 bmc_62 (U73807) formate dehydrogenase alpha subunit 17000-20000
182	3786 ENO_NITEU (O85348) ENOLASE (EC 42111) (2-PHOSPHOGLYCERATE DE
200	4084 TPMT_PSESJ (O86262) THIOPURINE S-METHYLTRANSFERASE
201	4093 FWDC_METJA (Q58571) TUNGSTEN-CONTAINING FORMYLMETHANOFURAN DEHY
202	4094 FTR_METBA (P55301) FORMYLMETHANOFURAN--TETRAHYDROMETHANOPTERIN
203	4104 MCH_METEX (O85014) N5,N10-METHENYLTETRAHYDROMETHANOPTERIN CYCLO
218	4296 ILVH_SALTY (P21622) ACETOLACTATE SYNTHASE ISOZYME III SMALL SUB
219	4298 ILVI_ECOLI (P00893) ACETOLACTATE SYNTHASE ISOZYME III LARGE SUB
226	4418 BIOB_SERMA (P36569) BIOTIN SYNTHASE (EC 2816) (BIOTIN
227	4419 BIOF_ERWHE (Q47829) 8-AMINO-7-OXONONANOATE SYNTHASE (EC 2314
228	4421 BIOH_ECOLI (P13001) BIOH PROTEIN
242	4544 GLGB_SYNY3 (P52981) 1,4-ALPHA-GLUCAN BRANCHING ENZYME (EC 241
243	4546 GLGA_ECOLI (P08323) GLYCOGEN SYNTHASE (EC 24121) (STARCH [BA
259	4800 ALKH_ERWCH (P38448) KHG/KDPG ALDOLASE [INCLUDES: 4-HYDROXY-2-OX
277	4885 DMPP_PSESP (P19734) PHENOL HYDROXYLASE P5 PROTEIN (EC 114137
278	4927 bmc_175 (AF309488) Methanol Dehydrogenase 2121-
279	4929 bmc_175 (U72662) mxaJ homolog 4000-
308	5148 PCPB_FLAS3 (P42535) PENTACHLOROPHENOL 4-MONOOXYGENASE (EC 114
310	5253 phenol 2-monooxygenase
315	5304 bmc_29 Methanol Dehydrogenase Subunit 1 Precursor 343-
316	5306 Bmc_209 Methanol Oxidation Protein 670-
318	5309 bmc_209 methanol dehydrogenase subunit 2 2066-
319	5310 bmc_209 Moxr Protein 2457-
330	5311 bmc_209 ORF 3800-
331	5312 bmc-209 mxaA gene product 4510-
343	5507 TMOC_PSEME (Q00458) TOLUENE-4-MONOOXYGENASE SYSTEM PROTEIN C
344	5544 ILVB_KLEPN (P27696) ACETOLACTATE SYNTHASE, CATABOLIC (EC 413
345	5546 ILVX_BACSU (Q04789) ACETOLACTATE SYNTHASE (EC 41318) (ACETOH
417	ribulose-bisphosphate carboxylase large chain (rbcA)
418	ribulose-bisphosphate carboxylase small chain (rbcB)
419	putative regulator of ribulose-bisphodphate carboxylase
420	phosphoglycerate kinase (cbbK)
421	glyceraldehyde-3-phosphate dehyrogenase (cbbG)
422	triosephosphate isomerase
423	sucrose-bisphosphate aldolase (fructose-1,-bisphosphate and sedoheptulose-
424	transketolase (tktl)

425	transketolase (tkt2), fragment
426	ribulosephosphate epimerase
427	ribose 5-phosphate isomerase (rpiA)
428	ribose 5-phosphate isomerase (rpiB)
429	phosphoribulokinase (cfxP)
430	hexulose-6-phoshate synthase (rmpA1)
431	hexulose-6-phosphate isomerase (rmpB1)
432	6-phospho-3-hexuloisomerase (rmpB2)
433	6-phosphofructokinase
434	transaldolase (rmpD)
435	D-arabino 3-hexulose 6-phosphate formaldehyde lyase
369	Putative glycolate oxidase iron-sulfur subunit
370	Putative glycolate oxidase iron-sulfur subunit
371	Putative glycolate oxidase subunit glcE
372	Putative glycolate oxidase subunit glcD
373	Putative phosphoglycolate phosphatase
347	2268 MOXX_PARDE (P29904) METHANOL UTILIZATION CONTROL REGULATORY PRO..
348	2269 MOXY_PARDE (P29905) METHANOL UTILIZATION CONTROL SENSOR PROTEIN..
349	5307 DHM1_METOR (P15279) METHANOL DEHYDROGENASE SUBUNIT 1 PRECURSOR.
350	5310 MOXR_METEX (P30621) MOXR PROTEIN (MXAR PROTEIN).
351	5407 PQQE_ACICA (P07782) COENZYME PQQ SYNTHESIS PROTEIN E (COENZYME
352	5408 PQQD_KLEPN (P27506) COENZYME PQQ SYNTHESIS PROTEIN D.
353	5409 PQQC_KLEPN (P27505) COENZYME PQQ SYNTHESIS PROTEIN C.
354	5410 PQQB_PSEFL (P55172) COENZYME PQQ SYNTHESIS PROTEIN B
355	5411 HMWC_DESVH (P24092) HIGH-MOLECULAR-WEIGHT CYTOCHROME C PRECURSO..
356	5416 DHB1_HUMAN (P14061) ESTRADIOL 17 BETA-DEHYDROGENASE 1
357	5426 MEMA_METCA (P22869) METHANE MONOOXYGENASE COMPONENT A ALPHA CHA
358	5429 MMOB_METCA (P18797) METHANE MONOOXYGENASE REGULATORY PROTEIN B

Table 2
Genes involved in the energy metabolism

SEQ ID NO	Putative names
28	549 PmoC3 (-1), bmc_16, 795
45	792 Bmc_24 Probable Methane Monooxygenase 45k Chain - Methylococcus
46	793 Bmc_24 PmoA2 31900-32500
47	795 Bmc_24 PmoC2 691 siste i contig
308	5148 PCPB_FLAS3 (P42535) PENTACHLOROPHENOL 4-MONOOXYGENASE (EC 114
310	5233 phenol 2-monooxygenase
343	5507 TMOC_PSEME (Q00458) TOLUENE-4-MONOOXYGENASE SYSTEM PROTEIN C
347	2268 MOXX_PARDE (P29904) METHANOL UTILIZATION CONTROL REGULATORY PRO..
348	2269 MOXY_PARDE (P29905) METHANOL UTILIZATION CONTROL SENSOR PROTEIN..
349	5307 DHM1_METOR (P15279) METHANOL DEHYDROGENASE SUBUNIT 1 PRECURSOR .
350	5310 MOXR_METEX (P30621) MOXR PROTEIN (MXAR PROTEIN).
351	5407 PQQE_ACICA (P07782) COENZYME PQQ SYNTHESIS PROTEIN E (COENZYME
352	5408 PQQD_KLEPN (P27506) COENZYME PQQ SYNTHESIS PROTEIN D.
353	5409 PQQC_KLEPN (P27505) COENZYME PQQ SYNTHESIS PROTEIN C.
354	5410 PQQB_PSEFL (P55172) COENZYME PQQ SYNTHESIS PROTEIN B
355	5411 HMWC_DESVH (P24092) HIGH-MOLECULAR-WEIGHT CYTOCHROME C PRECURSO..
356	5416 DHB1_HUMAN (P14061) ESTRADIOL 17 BETA-DEHYDROGENASE 1
357	5426 MEMA_METCA (P22869) METHANE MONOOXYGENASE COMPONENT A ALPHA CHA
358	5429 MMOB_METCA (P18797) METHANE MONOOXYGENASE REGULATORY PROTEIN B

Table 3

Genens involved in the metabolism of lipids

SEQ ID NO	
8	225 CAPI_STAAU (P39858) CAPI PROTEIN Bmc_5 Capi Protein 0-1000
17	376 ERY1_SACER Bmc_9 Ny: Putative Multi-Domain Beta Keto-Acyl Synthase
54	838 Bmc_26 fatty acid cis/trans isomerase 13000-15500
66	1154 OPT1_DROME (P91679) OLIGOPEPTIDE TRANSPORTER 1
67	1193 LPSE_RHIME (Q9R9N1) LIPOPOLYSACCHARIDE CORE BIOSYNTHESIS
68	1195 SPSC_BACSU (P39623) SPORE COAT POLYSACCHARIDE BIOSYNTHESIS
69	1198 PPX_ECOLI (P29014) EXOPOLYPHOSPHATASE
85	1884 MIAA_HAEIN (P44495) TRNA DELTA(2)-ISOPENTENYLPYROPHOSPHATE TRAN
87	1901 PGSA_HAEIN (P44528) CDP-DIACYLGLYCEROL--GLYCEROL-3-PHOSPHATE
90	1970 TAGA_BACSU (P27620) TEICHOIC ACID BIOSYNTHESIS PROTEIN A
91	1982 EPSA_BURSO (Q45407) EPS I POLYSACCHARIDE EXPORT OUTER MEMBRANE
92	2049 LPXB_HAEIN (P45011) LIPID-A-DISACCHARIDE SYNTHASE
93	2054 LPXA_CHRVI (Q46481) ACYL-[ACYL-CARRIER-PROTEIN]--UDP-N-ACETYLGL
110	2437 LPXD_ECOLI (P21645) UDP-3-O-[3-HYDROXYMYRISTOYL] GLUCOSAMINE N-
120	2651 CFA_ECOLI (P30010) CYCLOPROPANE-FATTY-ACYL-PHOSPHOLIPID SYNTHAS
126	2687 GTAB_BACSU (Q05852) UTP--GLUCOSE-1-PHOSPHATE URIDYLYLTRANSFERAS
127	2737 LOLD_XYLFA (P57032) LIPOPROTEIN RELEASING SYSTEM ATP-BINDING PR
131	2817 LCFA_BACSU (P94547) LONG-CHAIN-FATTY-ACID--COA LIGASE
142	3160 LGT_HAEIN (P44930) PROLIPOPROTEIN DIACYLGLYCERYL TRANSFERASE
146	3293 LIPB_PSEAE (Q9X6V9) LIPOATE-PROTEIN LIGASE B (EC 6---) (LIPO
147	3295 LIPA_ECOLI (P25845) LIPOIC ACID SYNTHETASE (LIP-SYN) (LIPOATE S
167	3507 UBIH_ECOLI (P25534) 2-OCTAPRENYL-6-METHOXYPHENOL HYDROXYLASE
174	3705 LPSE_RHIME (Q9R9N1) LIPOPOLYSACCHARIDE CORE BIOSYNTHESIS GLYCOS
175	3710 EPSB_BURSO (Q45409) EPS I POLYSACCHARIDE EXPORT PROTEIN EPSB
178	3742 LCFH_MYCTU (Q10776) PUTATIVE LONG-CHAIN-FATTY-ACID--COA LIGASE
181	3784 KDSA_RICPR (Q9ZE84) 2-DEHYDRO-3-DEOXYPHOSPHOOCTONATE ALDOLASE
186	3845 Bmc_85ny probable exopolysaccharide biosynthesis protein
187	3849 WZA_ECOLI (P76388) PUTATIVE POLYSACCHARIDE EXPORT PROTEIN WZA P
228	4215 ACO2_MOUSE (P13011) ACYL-COA DESATURASE 2 (EC 114995) (STEAR
230	4466 LPSE_RHIME (Q9R9N1) LIPOPOLYSACCHARIDE CORE BIOSYNTHESIS GLYCOS
231	4490 FABH_SALTY (O85139) 3-OXOACYL-[ACYL-CARRIER-PROTEIN] SYNTHASE I
232	4491 FABD_SALTY (O85140) MALONYL COA-ACYL CARRIER PROTEIN TRANSACYLA
234	4497 FABF_ECOLI (P39435) 3-OXOACYL-[ACYL-CARRIER-PROTEIN] SYNTHASE I
253	4628 Bmc_108 geranyltranstransferase
255	4633 Bmc_108 orf ved sqs
256	4635 Bmc_108/151 farnesyl-diphosphate farnesyltransferase
257	4637 Bmc_108 squalene-hopene cyclase
270	4819 KDGL_ECOLI (P00556) DIACYLGLYCEROL KINASE (EC 271107) (DAGK)
314	5260 KDTA_ECOLI (P23282) 3-DEOXY-D-MANNO-OCTULOSONIC-ACID TRANSFERAS
327	5396 LNT_PSEAE APOLIPOPROTEIN N-ACYLTRANSFERASE

Table 4
Other metabolically important genes

56	Putative ammonium monooxidase component A
57	Putative ammonium monooxidase, acetylene binding subunit
58	PROBABLE O-SIALOGLYCOPROTEIN ENDOPEPTIDASE. Involved in specific cleavage of glycosylated peptides. Outer membrane protein
36	serine hydroxymethyltransferase
37	serine-glyoxylate aminotransferase
38	putative hydroxypyruvate reductase
39	phosphoglycerate mutase
40	enolase
41	pyruvate kinase
42	oxaloacetate decarboxylase gamma subunit
43	oxaloacetate decarboxylase alpha subunit
44	oxaloacetate decarboxylase beta subunit
45	malate dehydrogenase
46	probably malyl-CoA synthase (mtkA)
47	probably malyl-CoA synthase (mtkB), partial
48	putative malate-CoA synthase (mlkA)
49	putative malate-CoA synthase (mlkB)
50	malyl-CoA lyase, partial. N-terminal
51	malyl-CoA lyase partial. C-terminal
52	malic enzyme, fragment
53	putative alpha-acetolactate synthase
54	putative alpha-acetolactate decarboxylase

Table 5

regulator genes

7	215 probable two-component response regulator PA4493
20	436 BARA_ECOLI (P26607) SENSOR PROTEIN BARA
21	438 bmc_12 transcription regulator AcoR 3000-4600
79	1606 DIMH_HUMAN (Q15392) DIMINUTO-LIKE PROTEIN
96	2064 CSRA_PSEAE (O69078) CARBON STORAGE REGULATOR HOMOLOG
102	2258 OMPR_ECOLI (P03025) TRANSCRIPTIONAL REGULATORY PROTEIN OMPR
124	2668 KDPD_ECOLI (P21865) SENSOR PROTEIN KDPD (EC 273-)
133	2897 FRZE_MYXXA (P18769) GLIDING MOTILITY REGULATORY PROTEIN
136	2948 CZCS_ALCEU (Q44007) SENSOR PROTEIN CZCS (EC 273-)
137	2949 CZCR_ALCEU (Q44006) TRANSCRIPTIONAL ACTIVATOR PROTEIN CZCR
138	2966 IRGA_VIBCH (P27772) IRON-REGULATED OUTER MEMBRANE VIRULENCE PRO
162	3435 CLPB_ECOLI (P03815) CLPB PROTEIN (HEAT SHOCK PROTEIN F841
163	3438 PHOR_KLEPN (P45608) PHOSPHATE REGULON SENSOR PROTEIN PHOR (EC 2
214	4285 CPXR_ECOLI (P16244) TRANSCRIPTIONAL REGULATORY PROTEIN CPXR
215	4286 CPXA_ECOLI (P08336) SENSOR PROTEIN CPXA (EC 273-)
220	4330 BASR_ECOLI (P30843) TRANSCRIPTIONAL REGULATORY PROTEIN BASR/PMRA
221	4336 BAES_ECOLI (P30847) SENSOR PROTEIN BAES (EC 273-)
326	5376 GACS_PSESY (P48027) SENSOR PROTEIN GACS (EC 273-)
363	4006 PRS1_ARCFU (O28303) PUTATIVE 26S PROTEASE REGULATORY SUBUNIT HO
364	4041 DEGP_SALTY (P26982) PROTEASE DO PRECURSOR

Table 6

M. capsulatus genes involved in transport and secretion

629 ID	
2	95 OPRM_PSEAE (Q51487) OUTER MEMBRANE PROTEIN OPRM PRECURSOR
5	225 CAPI_STAAU (P39858) CAPI PROTEIN Bmc_5 Capi Protein 0-1000
9	230 Bmc_5 probable outer membrane protein 1700-4000
16	314, bmc_7,TolC (P02930) OUTER MEMBRANE PROTEIN TOLC PRECURSOR
30	643 AMSH_ERWAM (Q46629) AMYLOVORAN EXPORT OUTER MEMBRANE PROTE
35	712 Bmc_23 (AF196490) High Affinity Phosphate Transport Protein Pstb [Caulobacter crescentus]
36	718 YQGH_BACSU (P46339) PROBABLE ABC TRANSPORTER PERMEASE PROTEIN
52	821; bmc_26 outermembrane
61	1096 SECD_ECOLI (P19673) PROTEIN-EXPORT MEMBRANE PROTEIN SECD
64	1124 EXBB_NEIMC (P95375) BIOPOLYMER TRANSPORT EXBB PROTEIN
66	1154 OPT1_DROME (P91679) OLIGOPEPTIDE TRANSPORTER 1
68	1195 SPSC_BACSU (P39623) SPORE COAT POLYSACCHARIDE BIOSYNTHESIS
71	1246 bmc_34 GspE 62460-63704: 5-297 (498)
72	1249 PILC_PSEAE (P22609) FIMBRIAL ASSEMBLY PROTEIN PILC
74	1381 LOLC_XYLFA (Q9PEF2) LIPOPROTEIN RELEASING SYSTEM TRANSMEMBRANE
75	1383 LOLD_NEIMA (P57030) LIPOPROTEIN RELEASING SYSTEM ATP-BINDING PR
78	1511 LOLA_NEIMB (P57068) OUTER-MEMBRANE LIPOPROTEINS CARRIER PROTEIN
88	1906 SECA_ECOLI (P10408) PREPROTEIN TRANSLOCASE SECA SUBUNIT
109	2421 AFAC_ECOLI (P53517) OUTER MEMBRANE USHER PROTEIN AFAC
108	2434 MopE
119	2649 MopD outermemb bmc_68
127	2737 LOLD_XYLFA (P57032) LIPOPROTEIN RELEASING SYSTEM ATP-BINDING PR
135	2929 EXBB_NEIMC (P95375) BIOPOLYMER TRANSPORT EXBB PROTEIN
138	2966 IRGA_VIBCH (P27772) IRON-REGULATED OUTER MEMBRANE VIRULENCE PRO
139	2979 IBEB_ECOLI (P77211) PROBABLE OUTER MEMBRANE LIPOPROTEIN IBEB P
141	3141 GSPA_AERHY (P45754) GENERAL SECRETION PATHWAY PROTEIN A
142	3160 LGT_HAEIN (P44930) PROLIPOPROTEIN DIACYLGLYCERYL TRANSFERASE
156	3382 MopC outermembrane
164	3440 PORF_PSESY MopB (P22263) OUTER MEMBRANE PORIN F PRECURSOR
172	3647 MALK_SALTY (P19566) MALTOSE/MALTODEXTRIN TRANSPORT ATP-BINDING
173	3651 LACF_AGRRD (P29823) LACTOSE TRANSPORT SYSTEM PERMEASE PROTEIN L
175	3710 EPSB_BURSO (Q45409) EPS I POLYSACCHARIDE EXPORT PROTEIN EPSB
177	3729 outer membrane hemin receptor XF0384
179	3759 PUTATIVE MEMBRANE PROTEIN hemaglutin
184	3841 CAPC_STAAU (P39852) CAPC PROTEIN
187	3849 WZA_ECOLI (P76388) PUTATIVE POLYSACCHARIDE EXPORT PROTEIN WZA P
193	3927 PROA_XANCP (P23314) EXTRACELLULAR PROTEASE PRECURSOR (EC
194	3937 FLBA_CAUCR (P21296) FLBA PROTEIN
206	4144 CAPD_STAAU (P39853) CAPD PROTEIN
207	4154 bmc_126,AbcA RFBB_MYXXA (Q50863) O-antigen export system atp-binding protein
225	4414 bmc_138 general secretion pathway protein d precursor (PulD)
233	4493 NODG_RHIS3 (P72332) NODULATION PROTEIN G
238	4518 LSPA_HAEIN (P44975) LIPOPROTEIN SIGNAL PEPTIDASE (EC 342336)
244	4549 Y021_SYNY3 (Q55682) PUTATIVE PROTEASE SLR0021 (EC 3421-)
245	4560 NODJ_BRAJA (P26025) NODULATION PROTEIN J
246	4561 NODI_RHIS3 (P72335) NODULATION ATP-BINDING PROTEIN I

Table 6

247	4566 TATC_AZOCH (P54085) SEC-INDEPENDENT PROTEIN TRANSLOCASE PROTEIN
248	4588 FEOB_SYNY3 (P73182) FERROUS IRON TRANSPORT PROTEIN B HOMOLOG
249	4594 COTA_BACSU (P07788) SPORE COAT PROTEIN A
265	4710 TOLR_PSEAE (P50599) TOLR PROTEIN
266	4711 TOLQ_PSEAE (P50598) TOLQ PROTEIN
282	4975 SLAP_CAUCR (P35828) S-LAYER PROTEIN extensin (pollen tubewall)
285	5082 bmc_196 pulD GSPD GENERAL SECRETION PATHWAY PROTEIN D PRECURSOR
290	5086 GSPL_XANCP (P34027) GENERAL SECRETION PATHWAY PROTEIN L
291	5088 GSPK_XANCP (P34026) GENERAL SECRETION PATHWAY PROTEIN K
292	5090 GSPJ_XANCP (P31740) GENERAL SECRETION PATHWAY PROTEIN J PRECURSOR
293	5091 GSPI_XANCP (P31738) GENERAL SECRETION PATHWAY PROTEIN I PRECURSOR
294	5092 GSPH_XANCP (P31736) GENERAL SECRETION PATHWAY PROTEIN H PRECURSOR
295	5093 GSPG_PSEAE (Q00514) GENERAL SECRETION PATHWAY PROTEIN G PRECURS
296	5095 GSPF_XANCP (P31744) GENERAL SECRETION PATHWAY PROTEIN F
297	5096 bmc_191 GspE GSPE_XANCP (P31742) GENERAL SECRETION PATHWAY PROTEIN
300	5112 IBEB_ECOLI (P77211) PROBABLE OUTER MEMBRANE LIPOPROTEIN IBEB PR
322	5340 RFA1_KLEPN (Q48475) O-ANTIGEN EXPORT SYSTEM PERMEASE PROTEIN RFBA
323	5342 ABCA_AERSA (Q07698) ABCA PROTEIN5342 AbcA
324	5366 Bmc_108 orfy_orfz+membranprotein squalene
346	5551 LOLD LIPOPROTEIN RELEASING SYSTEM ATP-BINDING

Table 7
Unknown genes

SEQ ID NO	
374	BMC101 COG0327
375	BMC131 COG0536
376	BMC22 COG0799
377	BMC22 COG0012
378	BMC29 COG1160
379	BMC36 COG1496
380	BMC4 COG0759
381	BMC59 COG0220
382	BMC61 COG0718
383	BMC61 COG0779
384	BMC71 COG1385
385	BMC71 COG0217
386	ydao.dna og
387	yaen.dna

C L A I M S

1. A DNA array comprising a plurality of polynucleotide or oligonucleotide probe spots stable associated with the surface of a solid support, wherein each polynucleotide probe spot, or alternatively a number of oligonucleotide probe spots, gives a representation of a plurality of M. captulatus genes.

2. DNA array in accordance with claim 1, wherein each of said unique polynucleotides does not significantly cross-hybridise under stringent conditions with a polynucleotide of any other polynucleotide probe composition on the array.

3. DNA array in accordance with claim 1, wherein said unique polynucleotides of said array have an average length of from 50 to 700 nucleotides (nt), more preferable 100 to 300 nt, and most preferable about 200 nt.

4. DNA array in accordance with claim 1, wherein said polynucleotide probe comprises a population of single stranded (identical) polynucleotides.

5. DNA array in accordance with claim 1, wherein said oligonucleotides have an average length of from 10 to 30 nucleotides (nt), or preferable about 20 nt.

6. DNA array in accordance with claim 1, wherein said array comprises at least 10, more preferable 20, more preferable 30, and most preferable substantial all of the M. captulatus genes listed in table 1.

7. DNA array in accordance with claim 1, wherein said array comprises at least 10, more preferable 20, more

preferable 30, and most preferable substantial all of the M. captulatus genes listed in table 2.

8. DNA array in accordance with claim 1, wherein said array comprises at least 10, more preferable 20, more preferable 30, and most preferable substantial all of the M. captulatus genes listed in table 3.

9. DNA array in accordance with claim 1, wherein said array comprises at least 10, more preferable 20, more preferable 30, and most preferable substantial all of the M. captulatus genes listed in table 4.

10. DNA array in accordance with claim 1, wherein said array comprises at least 10, more preferable 20, more preferable 30, and most preferable substantial all of the M. captulatus genes listed in table 5.

11. DNA array in accordance with claim 1, wherein said array comprises at least 10, more preferable 20, more preferable 30, and most preferable substantial all of the M. captulatus genes listed in table 6.

12. DNA array in accordance with claim 1, wherein said array comprises at least 10, more preferable 20, more preferable 30, and most preferable substantial all of the M. captulatus genes listed in table 7.

13. DNA array in accordance with claim 1, wherein said array comprises at least 50, more preferable 100, more preferable 300, and most preferable substantial all of the M. captulatus genes listed in tables 1 - 7, i.e. sequences SEQ ID NO 1 - SEQ ID NO 454.

14. DNA array in accordance with one of the claims 6 - 13, wherein the array further comprises unique M. capsulatus genes in accordance with SEQ ID NO 455 to SEQ ID NO 1840.

15. A kit for use in a hybridisation assay, said kit comprising a DNA array according to one of the claims 1 - 14.

16. Kit in accordance with claim 15, wherein said kit further comprises reagents for generating a labelled target polynucleotide sample.

17. Kit in accordance with claim 15, wherein said kit further comprises a hybridisation buffer.

18. Kit in accordance with claim 15, wherein said kit further comprises a wash medium.

19. DNA molecule, wherein said molecule comprising one of the sequences selected from the group comprising SEQ ID NO 1 to SEC ID NO 373.

20. Protein, wherein said protein is coded for by a DNA molecule comprises one of the sequences selected from the group comprising SEQ ID NO 1 to SEC ID NO 373.

21. A method for the determination of the differential expression of the genes of M. capsulatus due to an alteration in the incubation conditions from a firs incubation condition to a second incubation condition, wherein the expression of a plurality of sequences from the group comprising SEQ ID NO 1 to SEQ ID NO 454 is monitored on the two respective DNA arrays, and where expression of the first incubation condition is compared with the expression of the same genes of the second incubation condition.

22. A method according to claim 21, wherein the DNA arrays further comprises sequences selected from the group comprising SEQ ID NO 455 to 1840.

23. A method according to claim 21 or 22, wherein the alteration of incubation condition is selected from the group comprising alteration in temperature, alteration in pH, alteration in the presence of other organisms, the presence of chemicals, the presence of toxins, alteration in carbon source, alteration in energy source, alteration in trace element source, alteration in nitrogen source, alteration in phosphorous source and alterations in sulphur source.

24. A method according to claim 23, wherein the alteration in trace element source is an alteration in the level of metal ions.

25. A method according to claim 24, wherein the metal ions is copper ions.

High Cu^{2+} Low Cu^{2+}

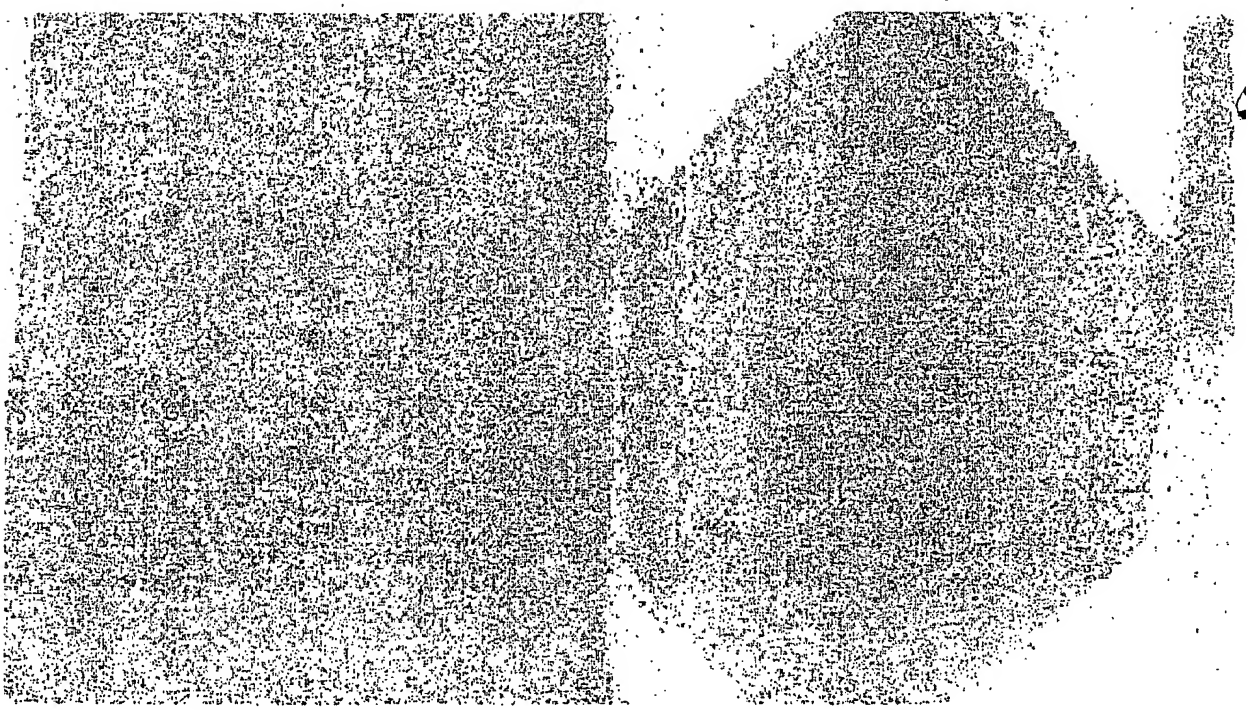

Fig. 1

SEQUENCE LISTING

<110> UNIFOB, Stiftelsen Universitetsforskning i Bergen
TIGR, The Institute for Genomic Rearch

<120> Method and system for the determination of gene expression in M. capsulatus

<130> UNIFOB -PCT case 1

<140> PCT/NO02/aaaaa
<141> 2002-01-14

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<213> Methylococcus capsulatus

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<211> 1572
<212> DNA
<213> Methylococcus capsulatus

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<211> 1464
<212> DNA
<213> Methylococcus capsulatus

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<210> 27
<211> 2130
<212> DNA
<213> Methylococcus capsulatus

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<210> 28
<211> 763
<212> DNA
<213> Methylococcus capsulatus

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<210> 29
<211> 1206
<212> DNA
<213> Methylococcus capsulatus

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<210> 30
<211> 1032
<212> DNA
<213> Methylococcus capsulatus

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<210> 31
<211> 1392
<212> DNA
<213> Methylococcus capsulatus

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<210> 32
<211> 714
<212> DNA
<213> Methylococcus capsulatus

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<210> 33
<211> 1092
<212> DNA
<213> Methylococcus capsulatus

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<210> 34
<211> 1080
<212> DNA
<213> Methylococcus capsulatus

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<212> DNA
<213> Methylococcus capsulatus

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<211> 1377
<212> DNA
<213> Methylococcus capsulatus

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<210> 37
<211> 1566
<212> DNA
<213> Methylococcus capsulatus

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<210> 38
<211> 534
<212> DNA
<213> Methylococcus capsulatus

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<210> 39
<211> 924
<212> DNA
<213> Methylococcus capsulatus

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<210> 40
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<212> DNA
<213> Methylococcus capsulatus

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<210> 41
<211> 2223
<212> DNA
<213> Methylococcus capsulatus

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gga 2223

<210> 42
<211> 1365
<212> DNA
<213> Methylococcus capsulatus

<400> 42
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<210> 43
<211> 1314
<212> DNA
<213> Methylococcus capsulatus

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<210> 44
<211> 1857
<212> DNA
<213> Methylococcus capsulatus

<400> 44
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<213> Methylococcus capsulatus

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<210> 48
<211> 666
<212> DNA
<213> Methylococcus capsulatus

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<210> 49
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<212> DNA
<213> Methylococcus capsulatus

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<211> 1770

<212> DNA
<213> Methylococcus capsulatus

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<212> DNA
<213> Methylococcus capsulatus

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<212> DNA
<213> Methylococcus capsulatus

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<210> 53
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<212> DNA
<213> Methylococcus capsulatus

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<210> 54
<211> 2349
<212> DNA
<213> Methylococcus capsulatus

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<210> 55
<211> 1212
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<213> Methylococcus capsulatus

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<211> 1155
<212> DNA
<213> Methylococcus capsulatus

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<211> 327
<212> DNA
<213> Methylococcus capsulatus

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gaggccggcc agctctacgg ccagttcgcg ctgaccagca ccggctgcct gggcacctgc 180
gatctcgggc cgaccgtcct ggtctatccg gagggcgtga tgtattccaa ggtgagtccg 240
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<210> 58
<211> 333
<212> DNA
<213> Methylococcus capsulatus

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<210> 59
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<212> DNA
<213> Methylococcus capsulatus

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<210> 60
<211> 687
<212> DNA
<213> Methylococcus capsulatus

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<210> 61

<211> 1848
<212> DNA
<213> Methylococcus capsulatus

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<210> 62
<211> 1017
<212> DNA
<213> Methylococcus capsulatus

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<210> 63
<211> 882
<212> DNA
<213> Methylococcus capsulatus

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<210> 64
<211> 675
<212> DNA
<213> Methylococcus capsulatus

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gagaccgccc accgc 675

<210> 65
<211> 819
<212> DNA
<213> Methylococcus capsulatus

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<210> 66
<211> 1455
<212> DNA
<213> Methylococcus capsulatus

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<211> 1098
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<213> Methylococcus capsulatus

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<210> 70
<211> 2394
<212> DNA
<213> Methylococcus capsulatus

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<212> DNA
<213> Methylococcus capsulatus

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<212> DNA
<213> Methylococcus capsulatus

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<210> 73
<211> 2172
<212> DNA
<213> Methylococcus capsulatus

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<210> 74
<211> 1245
<212> DNA
<213> Methylococcus capsulatus

<400> 74
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<210> 75
<211> 672
<212> DNA
<213> Methylococcus capsulatus

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<212> DNA
<213> Methylococcus capsulatus

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<213> Methylococcus capsulatus

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<211> 624
<212> DNA
<213> Methylococcus capsulatus

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<210> 79
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<212> DNA
<213> Methylococcus capsulatus

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<210> 80
<211> 1461
<212> DNA
<213> Methylococcus capsulatus

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<211> 654
<212> DNA
<213> Methylococcus capsulatus

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<210> 82
<211> 1053
<212> DNA
<213> Methylococcus capsulatus

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<210> 83
<211> 2043
<212> DNA
<213> Methylococcus capsulatus

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<210> 84
<211> 1272
<212> DNA
<213> Methylococcus capsulatus

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<213> Methylococcus capsulatus

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<212> DNA

<213> Methylococcus capsulatus

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<213> Methylococcus capsulatus

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<213> Methylococcus capsulatus

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<212> DNA
<213> Methylococcus capsulatus

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<212> DNA
<213> Methylococcus capsulatus

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<210> 97
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<212> DNA
<213> Methylococcus capsulatus

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<212> DNA
<213> Methylococcus capsulatus

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<211> 1791
<212> DNA
<213> Methylococcus capsulatus

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<211> 687
<212> DNA
<213> Methylococcus capsulatus

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<210> 101
<211> 1536
<212> DNA
<213> Methylococcus capsulatus

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<211> 729
<212> DNA
<213> Methylococcus capsulatus

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<210> 103
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<212> DNA
<213> Methylococcus capsulatus

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<210> 104

<211> 1098
<212> DNA
<213> Methylococcus capsulatus

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<210> 105
<211> 330
<212> DNA
<213> Methylococcus capsulatus

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<210> 106
<211> 900
<212> DNA
<213> Methylococcus capsulatus

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<210> 107
<211> 2448
<212> DNA
<213> Methylococcus capsulatus

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<213> Methylococcus capsulatus

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<213> Methylococcus capsulatus

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<212> DNA
<213> Methylococcus capsulatus

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<211> 2778
<212> DNA
<213> Methylococcus capsulatus

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<211> 1914
<212> DNA
<213> Methylococcus capsulatus

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<210> 114
<211> 651
<212> DNA
<213> Methylococcus capsulatus

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<210> 115
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<212> DNA
<213> Methylococcus capsulatus

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<210> 116
<211> 1311
<212> DNA
<213> Methylococcus capsulatus

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<213> Methylococcus capsulatus

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<210> 127
<211> 666
<212> DNA
<213> Methylococcus capsulatus

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gcagaa 666

<210> 128
<211> 930
<212> DNA
<213> Methylococcus capsulatus

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<210> 129
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<212> DNA
<213> Methylococcus capsulatus

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<213> Methylococcus capsulatus

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<210> 131
<211> 1530
<212> DNA
<213> Methylococcus capsulatus

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<210> 132
<211> 2595
<212> DNA
<213> Methylococcus capsulatus

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<213> Methylococcus capsulatus

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<210> 134
<211> 1497
<212> DNA
<213> Methylococcus capsulatus

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<211> 675
<212> DNA
<213> Methylococcus capsulatus

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<210> 136
<211> 1398
<212> DNA
<213> Methylococcus capsulatus

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<210> 137
<211> 684
<212> DNA
<213> Methylococcus capsulatus

<400> 137
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<210> 138
<211> 2127
<212> DNA
<213> Methylococcus capsulatus

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<211> 1308
<212> DNA
<213> Methylococcus capsulatus

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<210> 140
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<212> DNA
<213> Methylococcus capsulatus

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<210> 141
<211> 1647
<212> DNA
<213> Methylococcus capsulatus

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<212> DNA
<213> Methylococcus capsulatus

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<210> 143
<211> 1077

<212> DNA
<213> Methylococcus capsulatus

<400> 143
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<210> 144
<211> 1833
<212> DNA
<213> Methylococcus capsulatus

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<210> 145
<211> 1131
<212> DNA
<213> Methylococcus capsulatus

<400> 145
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<210> 146
<211> 621
<212> DNA
<213> Methylococcus capsulatus

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<210> 147
<211> 966
<212> DNA
<213> Methylococcus capsulatus

<400> 147
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<210> 148
<211> 1461
<212> DNA
<213> Methylococcus capsulatus

<400> 148
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<210> 149
<211> 1083
<212> DNA
<213> Methylococcus capsulatus

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<210> 150
<211> 1116
<212> DNA
<213> Methylococcus capsulatus

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aacgccgaat actaccggca acgggccagc gccggactga tcatctccga ggccacacag 180
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<210> 151
<211> 771
<212> DNA
<213> Methylococcus capsulatus

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<210> 152
<211> 1008
<212> DNA
<213> Methylococcus capsulatus

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<210> 153
<211> 612
<212> DNA
<213> Methylococcus capsulatus

<400> 153
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gaacgtgaag aa 612

<210> 154
<211> 870
<212> DNA
<213> Methylococcus capsulatus

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<210> 155
<211> 1080
<212> DNA
<213> Methylococcus capsulatus

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<210> 156
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<212> DNA
<213> Methylococcus capsulatus

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<212> DNA
<213> Methylococcus capsulatus

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<211> 420
<212> DNA
<213> Methylococcus capsulatus

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<210> 159
<211> 1365
<212> DNA
<213> Methylococcus capsulatus

<400> 159
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<210> 160
<211> 633
<212> DNA
<213> Methylococcus capsulatus

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<210> 161
<211> 1992
<212> DNA
<213> Methylococcus capsulatus

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<213> Methylococcus capsulatus

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<211> 2136
<212> DNA
<213> Methylococcus capsulatus

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<210> 164
<211> 1026

<212> DNA
<213> Methylococcus capsulatus

<400> 164
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aaggccaagg gcgtgaccaa ccagctctat ccgaagggct atggcgagga atatccgctg 960
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ggtgac 1026

<210> 165
<211> 1773
<212> DNA
<213> Methylococcus capsulatus

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<210> 166
<211> 756
<212> DNA
<213> Methylococcus capsulatus

<400> 166
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cagaacatcc gcaacagctc cttgcatggc aggacggaac ccctggtcca tatcgtcgat 180
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cggaccgtcg aaatctaccg tgccaacgtg atgcggaaaa tgcaggccga gaccctggcg 720
gacttggtgc gaatcgccct cctgctcgaa accgac 756

<210> 167
<211> 1203
<212> DNA
<213> Methylococcus capsulatus

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gagcgccagg cggctcccgc cggcgcgcgc gcgctggcac tggcccgtgg caccgcccgt 180
atcctggaga cgctgggcgt ttgggccgcg gtcgagccga aagccacacc gatccgccac 240
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cgc 1203

<210> 168
<211> 966
<212> DNA
<213> Methylococcus capsulatus

<400> 168
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gacctcaccg accaggccgc cgtccgcgcg tttttccagg ccgagaagcc cgaccaggtc 180
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cccttgcggg aaggcctcga acgaacctac caggcattcc tggaagagac cggcgagttc 960
gcgggg 966

<210> 169
<211> 1962
<212> DNA
<213> Methylococcus capsulatus

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<210> 170
<211> 1215

<212> DNA
<213> Methylococcus capsulatus

<400> 170
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gagagcctgg gaggc 1215

<210> 171
<211> 1143
<212> DNA
<213> Methylococcus capsulatus

<400> 171
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gtg 1143

<210> 172
<211> 1065
<212> DNA
<213> Methylococcus capsulatus

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<210> 173
<211> 861
<212> DNA
<213> Methylococcus capsulatus

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<210> 174
<211> 1110
<212> DNA
<213> Methylococcus capsulatus

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<213> Methylococcus capsulatus

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<212> DNA
<213> Methylococcus capsulatus

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<211> 2028
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<213> Methylococcus capsulatus

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<212> DNA
<213> Methylococcus capsulatus

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<212> DNA
<213> Methylococcus capsulatus

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<213> Methylococcus capsulatus

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<212> DNA
<213> Methylococcus capsulatus

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<211> 768
<212> DNA
<213> Methylococcus capsulatus

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<210> 185
<211> 2211
<212> DNA
<213> Methylococcus capsulatus

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<211> 1770
<212> DNA
<213> Methylococcus capsulatus

<400> 186
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<210> 187
<211> 507
<212> DNA
<213> Methylococcus capsulatus

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<210> 188
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<212> DNA
<213> Methylococcus capsulatus

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<210> 189
<211> 1545

<212> DNA
<213> Methylococcus capsulatus

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<210> 190
<211> 1554
<212> DNA
<213> Methylococcus capsulatus

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<210> 191
<211> 1029
<212> DNA
<213> Methylococcus capsulatus

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<210> 192
<211> 972
<212> DNA
<213> Methylococcus capsulatus

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<210> 193
<211> 1764
<212> DNA

<213> Methylococcus capsulatus

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<210> 194
<211> 1740
<212> DNA
<213> Methylococcus capsulatus

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<210> 195
<211> 972
<212> DNA
<213> Methylococcus capsulatus

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<210> 196
<211> 825
<212> DNA
<213> Methylococcus capsulatus

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<210> 197

<211> 1245
<212> DNA
<213> Methylococcus capsulatus

<400> 197
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<210> 198
<211> 936
<212> DNA
<213> Methylococcus capsulatus

<400> 198
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gacagcgcca gcgtcaagaa ggcggaggaa ctggtcagcc tgctgcggca gaccctcggt 480
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<210> 199
<211> 1323
<212> DNA
<213> Methylococcus capsulatus

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agg 1323

<210> 200
<211> 666
<212> DNA
<213> Methylococcus capsulatus

<400> 200
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tcggcc 666

<210> 201
<211> 810
<212> DNA
<213> Methylococcus capsulatus

<400> 201
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caaggcaagg gtgaaatcct gctggtcgct 810

<210> 202
<211> 960
<212> DNA
<213> Methylococcus capsulatus

<400> 202
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<210> 203
<211> 1272
<212> DNA
<213> Methylococcus capsulatus

<400> 203
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<210> 204

<211> 1101
<212> DNA
<213> Methylococcus capsulatus

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<210> 205
<211> 1800
<212> DNA
<213> Methylococcus capsulatus

<400> 205
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<212> DNA
<213> Methylococcus capsulatus

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<212> DNA
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<213> Methylococcus capsulatus

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<213> Methylococcus capsulatus

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<212> DNA
<213> Methylococcus capsulatus

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<212> DNA
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atcgccaccg ccgacaagcg ctatttccag ggcctgccca gcccctccgc cgccgccatc 480
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ttgctgttcg cggtgctgtt ttccaacccg ccgctggtgc tgttcctgtt cttcggcgcc 720
tatgccctgt cgggccccgc gttgacgctg gccctgctga aacggcggcg cggcgagcgg 780
cgcccg 786

<210> 217
<211> 1014
<212> DNA
<213> Methylococcus capsulatus

<400> 217
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caggtcgtgg tggggctgcg tccgggttcg gcttccgcca agaaggccga gaacgccggc 180
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ccggacgagc atcaggcccg cctctacaat gaacagatcg cgccgaacat caagcagggc 300
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accaccttcc gcgaagagac cgaaaccgat ctgttcggcg aacaggccgt cctgtgtggc 600
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cgcgacatga tgccgtggat caaggccaac cgcattgtgg acacgagcaa gaac 1014

<210> 218
<211> 489
<212> DNA
<213> Methylococcus capsulatus

<400> 218
atgcgtcaca tcatttccgt actgctcgaa aacgaatcgg gcgcgttgtc gcgcgttgcc 60
ggcctgttct ccgcccgcgg ctacaacatc gaatcgctca ccgtggcgcc aacccaggac 120
ccgaccctgt cgcgcatgac catcgtgact tccggcagcg atgaaatcat cgaacagatc 180
accaagcagc tgaacaagct gatcgacgtg gtcaagctgg tcgacctgtc ggaatcggcc 240
cacatcgagc gcgaactgat gatggtgaag gtacgcgcga ccaacggcgg gcgcgaggag 300
gtcaagcggc tggccgacat tttccgcggc aacatcatcg acgtgacgcc gaccagctac 360
gtgatcgagg tcaccggcga aaagtccaag ctggatgcct tcctgcaagc tctgcgggac 420
gaggacctca tcgaggtggt gcgctccggc accaccggca tcctgcgcgg ggagcgcgga 480
ctccacgtc 489

<210> 219
<211> 1728
<212> DNA
<213> Methylococcus capsulatus

<400> 219
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atcttcggct atccgggcgg tgcagtactg catatttacg atgcgctgtt caaacaggac 120
gatgtaaagc acatcctggt gcgccacgaa cagggcgcga cccacgcggc ggacggttac 180
gcccgctcca ccggcaaacc cggcgtggtc ctggtgactt cgggccccgg tgcgaccaat 240
gccgtcaccg gcatcgccac cgcctacatg gattcgatcc cgctggtggt catcacgggc 300
caggtgcccc tgcccgtcat cggcagcgac gccttccagg aggccgacat cgtcggtatc 360
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ttcaagaagg ccttctacat cgcgaccacg ggacgcccgg ggcccgtcgt gatcgacatc 480
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gatttcctca ccgatcccac cgaaaacgtc taccccatgg tcgaatccgg caaggcccat 1680
cacgagatgc ggctggcgcc cggtactgcg gttgacaggg agctcgcc 1728

<210> 220
<211> 672
<212> DNA
<213> Methylococcus capsulatus

<400> 220
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gccgaggatg gcttcgacct caccgttgcc gcgacgggaa cctacgccga cagtgccctg 120
cgcacccagg actacgatct ggtcatcctc gacctcggcc tgcccgacat cgacgggaaa 180
gaagtcctca ggcagttgcg ggtcagaaaa tcgccggtgc cggtcctcat cctgacggcc 240
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aagcctttcg agctgaggga actggaggcg cgggtgcggg cgctgatccg gcgcagccac 360
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ctcgacgatc tcggcattcg catcaggacg gtgcgcggcc tcggctacct gctggaacgg 660
cccgccggtg aa 672

<210> 221
<211> 1551
<212> DNA
<213> Methylococcus capsulatus

<400> 221
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ctggcggctt tgccgctgtt ggtcgccatc ggttcgaccg tcggcgccgt ggatgatctc 120
gccgcgcagt cccgaaaaac cgtctattcc gtcgcgcagc tcagccagaa aagcttcatg 180
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acccgcccga tccggcaact ggaatccgcg atccgtcagt tggggagcgg cgattaccag 720
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catgaggtca agacaccact cgcgaccatc cacgagggca cggggctgct ggcggatgaa 900
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cagcggctcg agcgcttgat cacggcgctg atcaacttca gtcaggccaa tgccgacccg 1020
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ctggccatcg tccgcgagtg cgtcatgagc caccatggca gcgtcgaact gctggatccg 1440
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cggttgcgcg tgcgaatttc atttcctcgg caaggagaac ccgccgatgt c 1551

<210> 222
<211> 1810
<212> DNA
<213> Methylococcus capsulatus

<400> 222
abcatcagcg gcgcacggcg tgcaccgcca ccgcttccgg cacgctcgaa tagccgaatt 60
gcatcgcgta gaggtcggca taaccgcccc gcgccgccat gagctgggca tgggtgccgc 120
actcgatgat acgcccgccg cgcatcacgc aaatctggtc cgcattctgg atggtggaca 180
gccggtgcgc gatcaccagt gtcgtccggt tctgcatcag gacttccagc gcctgctgca 240
cgtagcgctc ggattccgcg tccagcgccg aggtcgcctc gtccaggatc agaatagggg 300
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tgccctgctg gccgacgagg gtatcgaatc cttgcggcag cgtctctatg aaatccagcg 420
cattcgccgc ccgcgcggcc tcgcgcacgg catcgaggcc caccctgtcc aggcagccgt 480
aggcgatgtt gctggcaacg gtatcgttga acagcgtcac ttcctgcccg acataagcaa 540
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cgcgcaggac ggaaaggccg atcagcatca gggacacctg gcgcagcacc gtcggatcgt 1620
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cggcataggc gatcatcgcc accacggcga cgcagaacga cctccagtac ggaaatccat 1740
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aatgtttcat 1810

<210> 223
<211> 1452
<212> DNA
<213> Methylococcus capsulatus

<400> 223

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atggcctata gcttgttgat catcgaagac gagaaactgc tcggctcgga actggtccgg 120
cactacgaaa gggccggctg ggacgtcgat tgggccaaga cgctggccga agcgcgcaac 180
ctgttcacca agaaagcggt cgacccgctg ctggtactgt ccgaccgtag cctgccggac 240
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cgctccgccc aggcgcagcg ccgtctgctc gaacaggcgc aggaacggca ccgccgctat 480
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aaggaaaccg cc 1452

<210> 224
<211> 975
<212> DNA
<213> Methylococcus capsulatus

<400> 224
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tcctcgacgg cggacgcctt gtttacgtcc cagccgggta tcagcaagca gatcaagctg 120
ctggaggagg agctgggaat ctccatcttc gcccgcagcg gcaaacattt gaccgagatc 180
acgccagccg gcaaatacgt cgtggaactc gctggacaga ttctcagcaa ggttcaggac 240
atccgcagcg tcgcccagga attccgtgac aaccgggtcg gttcgctatc cattgccacc 300
acccataccc aggctcgcta tgccttgccg ccggtggtgc gtgaattcat gcagcgttat 360
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acgctgcccg tgcgg 975

<210> 225
<211> 1575
<212> DNA
<213> Methylococcus capsulatus

<400> 225
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ggcaacgtgc tgcgcatcct gccgatcgaa cgcctcaacg ccatcctcgc cgtggctcct 120

gagatgcatc tcctgcacga agtgcaggac tggatcgaac ggctcgaccg ctacaacacc 180
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ttccgccgca agctgaccaa cctatacaga ggcgagccgg acgcccagcc ggcggcggtg 1560
gagccttcga cgccg 1575

<210> 226
<211> 1044
<212> DNA
<213> Methylococcus capsulatus

<400> 226
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ctgcgcatgg cgggcttggg ctgc 1044

<210> 227
<211> 1161
<212> DNA
<213> Methylococcus capsulatus

<400> 227
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<213> Methylococcus capsulatus

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<210> 229
<211> 1278
<212> DNA
<213> Methylococcus capsulatus

<400> 229
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<210> 230
<211> 1119
<212> DNA
<213> Methylococcus capsulatus

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<210> 231
<211> 798
<212> DNA
<213> Methylococcus capsulatus

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<210> 232
<211> 954
<212> DNA
<213> Methylococcus capsulatus

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<210> 233
<211> 735
<212> DNA
<213> Methylococcus capsulatus

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<210> 234
<211> 1239
<212> DNA
<213> Methylococcus capsulatus

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<210> 235
<211> 828
<212> DNA
<213> Methylococcus capsulatus

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<210> 236
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<212> DNA
<213> Methylococcus capsulatus

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<210> 237
<211> 1539
<212> DNA
<213> Methylococcus capsulatus

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<210> 238
<211> 474
<212> DNA
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<210> 239
<211> 1023
<212> DNA
<213> Methylococcus capsulatus

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<210> 240
<211> 1548
<212> DNA
<213> Methylococcus capsulatus

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<212> DNA
<213> Methylococcus capsulatus

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<212> DNA
<213> Methylococcus capsulatus

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<212> DNA
<213> Methylococcus capsulatus

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<211> 981
<212> DNA
<213> Methylococcus capsulatus

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<210> 245
<211> 981
<212> DNA
<213> Methylococcus capsulatus

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<210> 246
<211> 987
<212> DNA
<213> Methylococcus capsulatus

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<210> 247
<211> 1056
<212> DNA
<213> Methylococcus capsulatus

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<210> 248
<211> 1785
<212> DNA
<213> Methylococcus capsulatus

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<210> 249
<211> 1560
<212> DNA
<213> Methylococcus capsulatus

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<212> DNA
<213> Methylococcus capsulatus

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<210> 251

<211> 2343
<212> DNA
<213> Methylococcus capsulatus

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<210> 252
<211> 1887
<212> DNA
<213> Methylococcus capsulatus

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<210> 253
<211> 903
<212> DNA
<213> Methylococcus capsulatus

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<210> 254
<211> 1920
<212> DNA
<213> Methylococcus capsulatus

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<210> 255
<211> 1116
<212> DNA
<213> Methylococcus capsulatus

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<210> 256
<211> 1089

<212> DNA
<213> Methylococcus capsulatus

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<210> 257
<211> 1974
<212> DNA
<213> Methylococcus capsulatus

<400> 257
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<213> Methylococcus capsulatus

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<210> 259
<211> 807
<212> DNA
<213> Methylococcus capsulatus

<400> 259
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<210> 260
<211> 858
<212> DNA
<213> Methylococcus capsulatus

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<210> 261
<211> 474
<212> DNA
<213> Methylococcus capsulatus

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<210> 262
<211> 906
<212> DNA
<213> Methylococcus capsulatus

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<210> 263
<211> 2295
<212> DNA
<213> Methylococcus capsulatus

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gcccacgcac gggcctttac cattgcgaag gcggcgcggc tggacgtggt gcaggacatt 180
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ttgttatttc gaaga 2295

<210> 264
<211> 471
<212> DNA
<213> Methylococcus capsulatus

<400> 264

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aaagtctatg ccgctattca tcagttcggc gggtccgcgg gacgtagcca acgaacgacg 360
attccagcac gtccctatct gccgatgacg gccaaaggcg agctgacgcc ccaggccaga 420
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<210> 265
<211> 438
<212> DNA
<213> Methylococcus capsulatus

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<210> 266
<211> 816
<212> DNA
<213> Methylococcus capsulatus

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<210> 267
<211> 1203
<212> DNA
<213> Methylococcus capsulatus

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<210> 268
<211> 822
<212> DNA
<213> Methylococcus capsulatus

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<210> 269
<211> 633
<212> DNA
<213> Methylococcus capsulatus

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<210> 270
<211> 1083

<212> DNA
<213> Methylococcus capsulatus

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<213> Methylococcus capsulatus

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<210> 273
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<212> DNA
<213> Methylococcus capsulatus

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<210> 274
<211> 930
<212> DNA
<213> Methylococcus capsulatus

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<210> 275
<211> 402
<212> DNA
<213> Methylococcus capsulatus

<400> 275

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<210> 276
<211> 711
<212> DNA
<213> Methylococcus capsulatus

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<210> 277
<211> 1536
<212> DNA
<213> Methylococcus capsulatus

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<210> 278
<211> 2028
<212> DNA
<213> Methylococcus capsulatus

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<213> Methylococcus capsulatus

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<210> 280
<211> 1896
<212> DNA
<213> Methylococcus capsulatus

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<210> 281
<211> 2424
<212> DNA
<213> Methylococcus capsulatus

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<210> 282
<211> 1452
<212> DNA
<213> Methylococcus capsulatus

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<210> 283
<211> 615
<212> DNA
<213> Methylococcus capsulatus

<400> 283
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cgccaaccca gcgtt 615

<210> 284
<211> 1122
<212> DNA
<213> Methylococcus capsulatus

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<210> 285
<211> 4029
<212> DNA
<213> Methylococcus capsulatus

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<210> 286
<211> 1122
<212> DNA
<213> Methylococcus capsulatus

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gaactgcggc gccgggcgcg tcccccgggg agcagcgggc gc 1122

<210> 287
<211> 624
<212> DNA
<213> Methylococcus capsulatus

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gaggcgcgca gcccttcact ggct 624

<210> 288
<211> 830

<212> DNA
<213> Methylococcus capsulatus

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<210> 289
<211> 618
<212> DNA
<213> Methylococcus capsulatus

<400> 289
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atgtcgcaga aagcgccc 618

<210> 290
<211> 1116
<212> DNA
<213> Methylococcus capsulatus

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<210> 291
<211> 1107
<212> DNA
<213> Methylococcus capsulatus

<400> 291
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<213> Methylococcus capsulatus

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<213> Methylococcus capsulatus

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<211> 465
<212> DNA
<213> Methylococcus capsulatus

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<210> 295
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<212> DNA
<213> Methylococcus capsulatus

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<211> 1215
<212> DNA
<213> Methylococcus capsulatus

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<210> 297
<211> 789
<212> DNA
<213> Methylococcus capsulatus

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<211> 1086
<212> DNA
<213> Methylococcus capsulatus

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<210> 299
<211> 3204

<212> DNA
<213> Methylococcus capsulatus

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<211> 927
<212> DNA
<213> Methylococcus capsulatus

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<213> Methylococcus capsulatus

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<211> 402
<212> DNA
<213> Methylococcus capsulatus

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<210> 303
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<213> Methylococcus capsulatus

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<213> Methylococcus capsulatus

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<213> Methylococcus capsulatus

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<211> 519
<212> DNA
<213> Methylococcus capsulatus

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<210> 312
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<213> Methylococcus capsulatus

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<210> 313
<211> 1524
<212> DNA
<213> Methylococcus capsulatus

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